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藥學博士 學位論文

강력한 항암 활성 Isocarbostyril 알칼로이드인 (+)-*trans*-Dihydronarciclasine의 입체선택적 전합성

Stereoselective Total Synthesis of (+)-*trans*-Dihydronarciclasine, a Potent Anticancer Isocarbostyril Alkaloid

2014년 2월

서울大學校 大學院

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指導敎授 金 相 熙

이 論文을 藥學博士 學位論文으로 提出함

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2014年 **2**月

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Abstract

We have achieved a highly stereoselective and efficient total synthesis of *trans*-dihydronarciclasine from a readily available chiral starting material. Our scheme defines two of the five stereogenic centers of the natural product by an amino acid ester-enolate Claisen rearrangement. The other three stereogenic centers are created in a highly stereocontrolled fashion via a six-membered-ring vinylogous ester intermediate, which is generated from the γ,δ-unsaturated ester functional group of Claisen rearrangement product in an efficient three-step sequence. This concise total synthesis exemplifies the use of a highly regioselective Friedel-Crafts-type cyclization to form the B-ring via an isocyanate intermediate derived from an *N*-Boc group, which is superior to the conventional method using an imino triflate intermediate. This mild and regioselective reaction conditions are also applicable for synthesis of various substituted isoquinolin-1-ones, β-carbolines, thiophen fused ring systems and tetrahydrobenzoazepin-1-ones. Acid additives, such as $BF_3 \cdot Et_2O$, extend the application of the method to substrates bearing less nucleophilic aryl moieties by enhancing the Friedel-Crafts-type cyclization of isocyanate intermediates.

Key word: Acid-mediated cyclization, Antitumor agents, Ireland-Claisen rearrangement, Natural products, Total synthesis

Student Number: 2007-21826

Contents

I. Introduction

Based on their potent and selective anticancer activity as well as their unique structural features, *Amaryllidaceae* isocarbostyril alkaloids have been an attractive synthetic target for the last two decades.[1,2] Some representative members of this class of natural products are *trans*-dihydronarciclasine (**1**, Figure 1), pancratistatin (**2**), lycoricidine (**3**), and narciclasine (**4**). These natural isocarbostyrils exhibit potent cytotoxicity in the NCI 60 human tumor cell line panel with GI_{50} values in the nanomolar range.[3] Although *trans*-dihydronarciclasine has far greater anticancer activity than the intensively investigated pancratistatin (**2**) and other congeners,[3b] less effort has been devoted to biological and synthetic studies on *trans*-dihydronarciclasine until recently.[4]

The isolation of (+)-**1** from the Chinese medical plant *Zephyranthes candida* was reported in 1990.[5] Interestingly, it was produced synthetically long before its isolation from natural sources, through hydrogenation of narciclasine (**4**) with low diastereoselectivity.[6] The first total synthesis of the racemate was reported by Cho in 2007,[4a] which involved a Diels-Alder cycloaddition of 3,5-dibromo-2-pyrone for the preparation of functionalized C-ring. The first enantioselective synthesis by Studer appeared in 2008,[4b] in which the required absolute stereochemistry of C-ring was introduced by a Cu-catalyzed enantioselective nitroso Diels-Alder reaction. Both syntheses employed Banwell's modified Bischler-Napieralski reaction at a late stage of the sequence for closure of the B-ring.

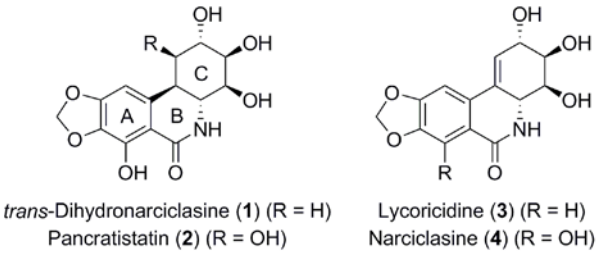


Figure 1. Chemical structures of compounds **1**−**4**.

Herein, we wish to describe a short and highly stereocontrolled total synthesis of (+)-**1** by a strategy that is unique as compared to other previous syntheses of *Amaryllidaceae* isocarbostyril alkaloids. Our route is characterized by the use of an *N*-Boc group first to steer the stereochemical course of a Claisen rearrangement, and then to generate an isocyanate intermediate for a highly regioselective Friedel-Crafts-type B-ring cyclization. This approach is superior to using the conventional Bischler-Napieralski-type B-ring cyclization, especially in the sense of regioselectivity.

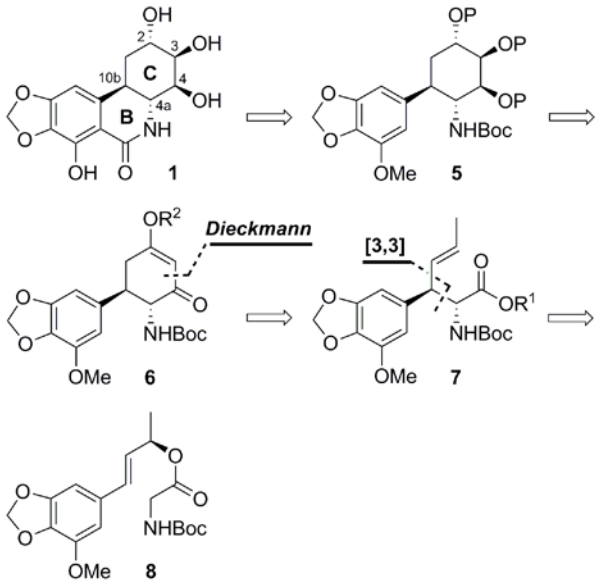
II. Results and Discussion

II-1. Retrosynthetic Analysis

As shown in Scheme 1, we planned to construct the B-ring of **1** at a late stage of the synthesis, similarly to many other *Amaryllidaceae* isocarbostyril synthetic approaches. We envisioned construction of the B-ring could be achieved by utilizing the *N*-Boc carbamate group in **5**, where this group is also essential for attaining high stereocontrol in the subsequent transformations (*vide infra*). Our strategy was premised on the selective transformation the *β*-keto enol ether function of **6** to the three contiguous hydroxyl groups in the C-ring of **5**. We expected that cyclic vinylogous ester **6** could be obtained regioselectively from the *γ*,*δ*-unsaturated ester **7** via regioselective Wacker oxidation, Dieckmann condensation, and regioselective vinylogous ester formation. We further envisioned that an ester enolate Claisen rearrangement of the Boc-protected amino acid allylic ester **8** would provide the γ,δ-unsaturated *α*-amino ester **7**.[7] In this transformation, the required stereochemistry of the two contiguous stereocenters at C-4a and C-10b could be installed with chirality transfer from a preformed chiral center in substrate **8** via a chair-like transition state. The Boc group was chosen as the amino protecting group because the stereoselectivity of ester enolate Claisen rearrangements of Boc-protected amino esters is generally superior to that of other carbamate-protected amino esters.[8] In addition, the bulkiness of the Boc group was expected to promote high reaction

selectivity through steric interactions or conformational reinforcement, especially in the introduction of the three contiguous hydroxyl group stereocenters.

Scheme 1. Retrosynthetic analysis of *trans*-dihydronarciclasine (**1**).



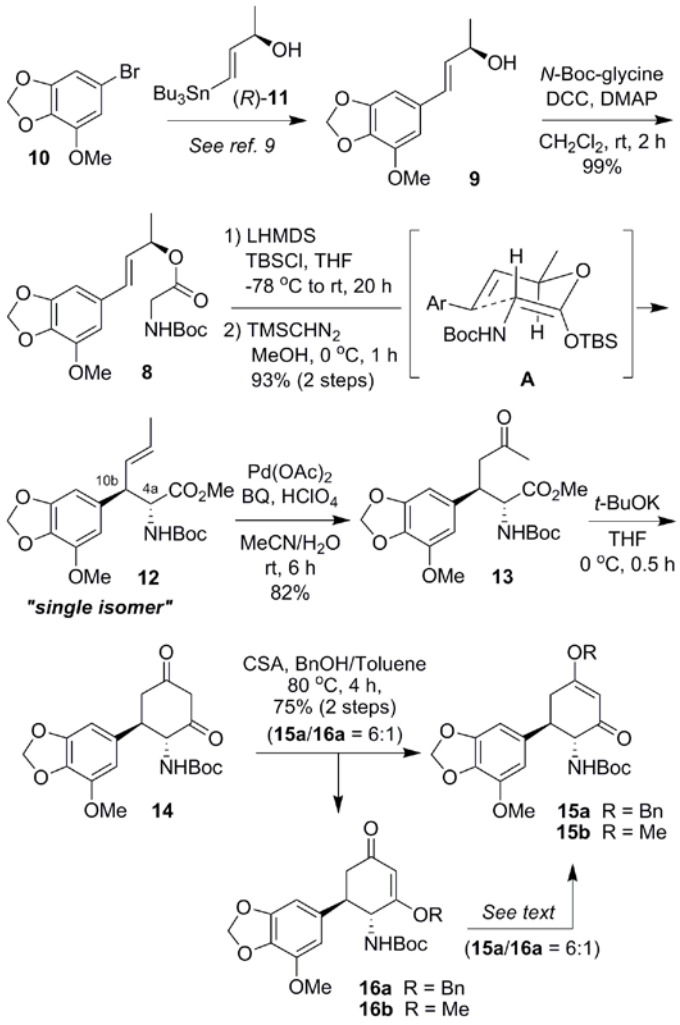
II-2. A-C Ring System Synthesis

As illustrated in Scheme 2, the synthesis was initiated by preparing Claisen substrate **8** from the enantiomerically enriched allylic alcohol **9**. The synthesis of **9** from the aryl bromide **10** and chiral building block (*R*)-**11** (>99% *ee*) was previously reported by us in

the total synthesis of **2**.[9] Allylic alcohol **9** was then coupled with *N*-Boc-glycine to provide the chiral allylic amino acid ester **8**. After some experimentation, we identified conditions that led to the formation of the desired rearranged product **12** in excellent stereoselectivity and yield. Deprotonation of **8** at −78 °C with LHMDS in THF in the presence of TBSCl resulted in the formation of the intermediate (*Z*)-silyl ketene acetal, which underwent Claisen rearrangement upon gradual warming to room temperature to afford **12** (93%) after treatment with TMS-diazomethane.[10] A single diastereomer was observed by NMR and HPLC analysis. The absolute configurations of the two new stereocenters were assumed to be 4a*R* and 10b*R* by invoking chair transition state **A** for the rearrangement, and these configurations were ultimately confirmed through conversion to the final natural product.

Efforts were next directed toward forming the C-ring by a two-step process that began with regioselective oxidation of the internal olefin to afford methyl ketone **13**. The resulting intermediate could then undergo Dieckmann condensation to give cyclic *β*-diketone **14**. In the event, highly regioselective (8:1) Wacker oxidation of olefin **12** could be achieved in 82% yield with $Pd(OAc)_2$ and benzoquinone (BQ).[11] Condensation of **13** using *t*-BuOK in THF provided the desired *β*-diketone **14**, which was used directly in the next step without further purification.[12]

Scheme 2. Synthesis of intermediate **15**.



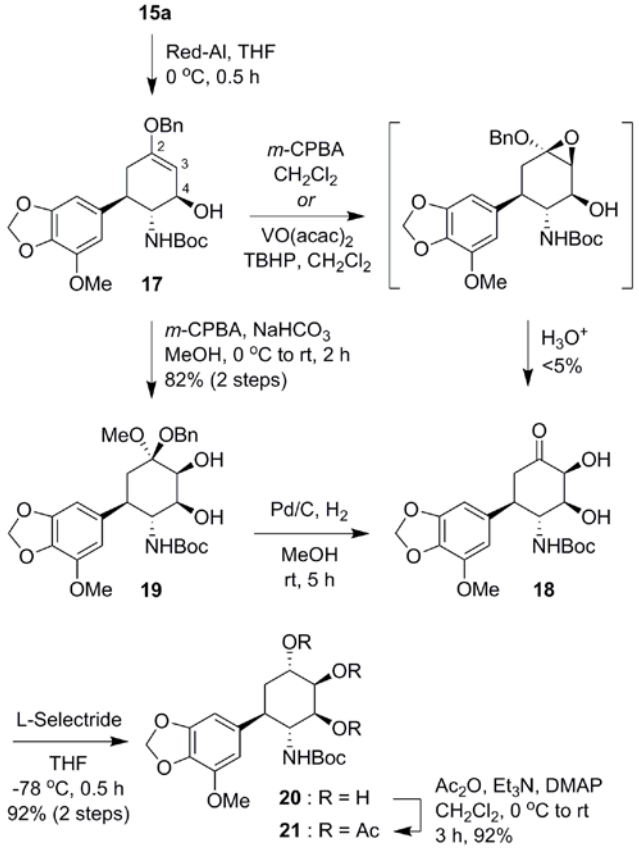
II-3. C-Ring Functionalization

Our approach to functionalize the C-3 position was to convert cyclic β-diketone moiety

of **14** to the corresponding vinylogous ester by enol etherification. The regiochemical outcomes of etherification of asymmetric cyclic *β*-diketones are often difficult to predict, and mixtures of the two possible products are frequently produced.[13] However, we envisioned that enol etherification of **14** would be regioselective under thermodynamic conditions, since vinylogous ester **15** was expected to be thermodynamically more stable than its regioisomer **16** primarily due to the lower steric strain. Some support was obtained from our computational modeling studies, which predicted that **15b** would be more stable than **16b** by 1.36 kcal/mol.[14] As expected, treatment of crude **14** with benzyl alcohol and a catalytic amount of camphorsulfonic acid in toluene at 80 °C led to the selective formation of vinylogous benzyl ester **15a** (64% yield from **13**), along with a minor amount of its regioisomer **16a** (6:1). **16a** could be recycled by chromatographic separation followed by resubjection to the above etherification conditions to isomerize it back to the 6:1 mixture in favor of **15a**.[15]

Next, our study focused on the selective conversion of the *β*-keto enol ether function of **15a** into a triol (Scheme 3). First, the carbonyl group of **15a** was stereoselectively reduced with Red-Al to give exclusively the required 4*β*-hydroxy group. Since allylic alcohol **17** was unstable,[13c,16] it was immediately used in the next step without chromatographic purification. Dihydroxylation of the enol ether **17** under the Upjohn dihydroxylation conditions (OsO_4, NMO)[17] afforded exclusively the undesired C3-*α* stereoisomer (79% from **15a**) instead of **18**. Even under the hydroxy-directed dihydroxylation conditions of Donohoe,[18] the same undesired isomer was formed (76%).

Scheme 3. Introduction of the stereocenters in the C ring.



On the other hand, epoxidation of the enol ether **17** by using *m*-CPBA or $VO(acac)_2$/TBHP system[19] did occur on the desired β-face of the molecule to produce the α-hydroxy ketone **18** with the desired C3 stereochemistry, but in a disappointingly low yield (<5%). To overcome the problem of low yield, the domino epoxidation-methanolysis protocol was employed.[20] Epoxidation with *m*-CPBA in MeOH in the presence of $NaHCO_3$ provided mixed ketal **19** as a single diastereoisomer in 82% yield (2 steps) from **15a**. Since α-hydroxy ketals are prone to rearrange under acidic conditions,[21]

the deketalization of **19** was effected gently by catalytic hydrogenation of the benzyl group to give ketone **18**. Dihydroxyketone **18** itself was also found to be unstable,[22] and readily decomposed to unidentified polar material. Thus, the best approach was to treat crude ketone **18** directly with the sterically demanding L-Selectride to give triol **20** as the sole stereoisomer in 92% overall yield from **19**.[23] Triol **20** was then protected to give triacetate **21** (92%).

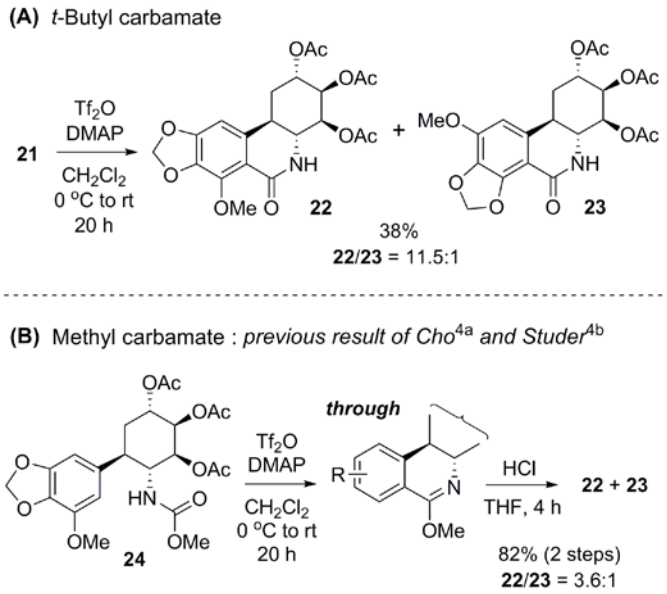
II-4. B-Ring Construction under Banwell's Modified Bischler-Napieralski Reaction Conditions

After completing the functionalization of the C-ring, we turned our attention to the construction of the B-ring to complete the total synthesis. Banwell's modified Bischler-Napieralski reaction,[24] which is thought to proceed via an imino triflate intermediate, has been used widely for closure of the B-ring in the synthesis of *Amaryllidaceae* alkaloids including *trans*-dihydronarciclasine (**1**) and pancratistatin (**2**). However, literature examples of this reaction show it only to be effective for primary alkyl carbamate substrates.[2c-e] Thus, we were uncertain at that time that the Banwell procedure would be applicable to B-ring formation using the *N*-Boc group in our case.

Under the standard Banwell's reaction conditions (Tf_2O/DMAP = 5/3 molar ratio, 0 °C), we were able to obtain the desired cyclization product **22** along with a minor amount of

the regioisomer **23** from the *N*-Boc carbamate **21**, but in a very low yield (38%) (Scheme 4). Interestingly, although the chemical yield was much lower (38% vs. 82%), the degree of regioselectivity in the B-ring formation was considerably higher than in the reported case in which Banwell's modified Bischler-Napieralski reaction conditions were applied to the corresponding methoxycarbonyl compound **24** (11.5:1 vs. up to 3.6:1).[4a,b] This remarkable regioselectivity difference between the cyclization of substrate **21** and **24** under the same reaction conditions implied that the two cycloaddition reactions might proceed via different intermediates.

Scheme 4. B-ring construction under Banwell's reaction conditions.



Recently, Schofield and co-workers have observed that upon treatment with 2.0 equiv of

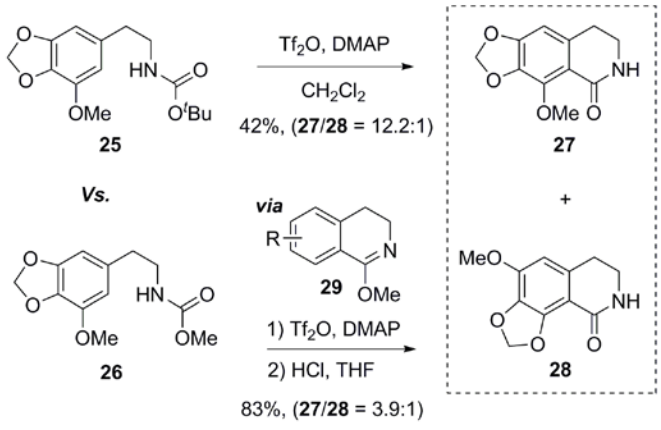
Tf_2O and 2.2 equiv of Et_3N or pyridine, *N*-Boc protected phenylalanine ester underwent dimerization to form a urea, most probably via an isocyanate intermediate.[25] This observation suggested the possibility that under Banwell's acidic reaction conditions, the *N*-Boc carbamate of **21** was converted to an isocyanate through loss of its acid-labile *t*-butyl group and dehydration, and this in situ generated isocyanate underwent intramolecular Friedel-Crafts-type cyclization. Although there have been several reports of isocyanates being used in Friedel-Crafts-type cyclization,[26] no examples of the intramolecular Friedel-Crafts capture of an isocyanate intermediate generated from *N*-Boc carbamates have been reported.[27] Isocyanates could be prepared by several methods, such as from an amine by treatment with phosgene[26a] or its equivalent including $(Boc)_2O$/DMAP,[26b] from an acid or amide utilizing Curtius or Hoffmann rearrangement,[26c,d] and from a carbamate by treatment with dehydrating reagents.[28] However, only a few examples of the direct conversion of *N*-Boc carbamate to an isocyanate have been reported.[28a,b]

II-5. Model studies and Optimization of B–Ring Construction

Based on the observation of Schofield and our initial results under Banwell's reaction conditions, our studies began with the reagent combination of Tf_2O and base for Friedel-Crafts-type reactions of *N*-Boc carbamate substrates via isocyanate intermediateds. *N*-Boc

carbamate **25** (Scheme 5) was chosen as an initial model substrate. Before identifying the optimal reaction conditions for our purposes, we first examined the chemical behavior differences between *N*-Boc carbamate substrate **25** and the corresponding *N*-Moc substrate **26** under Banwell's modified Bischler-Napieralski reaction conditions (Scheme 5). Under the Banwell conditions, *N*-Boc substrate **25** provided dihydroisoquinolinone **27** along with the minor regioisomeric product **28** in 42% combined yield and 12.2:1 regioselectivity. On the other hand, the *N*-Moc substrate **26** provided a methyl imidate **29**, which upon hydrolysis with 3 M HCl afforded **27** and **28** in a higher combined yield (83%) but with much lower regioselectivity (3.9:1). These results are very similar to those observed for the corresponding, more complex substrates **21** and **24**.

Scheme 5. Model Studies of B-ring Construction

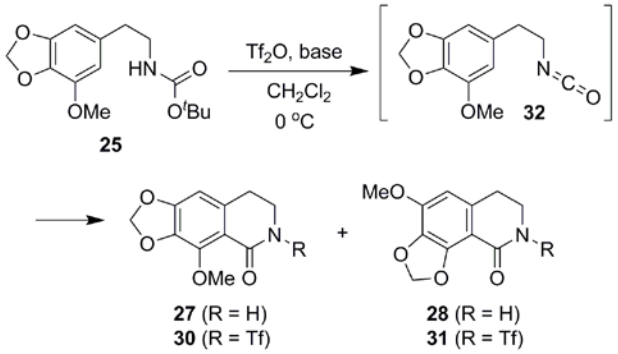


When DMAP in Banwell's reagent combination was replaced by the less basic pyridine and 2-chloropyridine,[29] *N*-Boc carbamate **25** provided **27** and **28** as well as their *N*-

triflated derivatives **30** and **31** (Table 1, entries 2 and 3). The combined yield of cyclized products was increased, and the high regioselectivity was maintained (entries 2 and 3 vs. entry 1). To avoid the *N*-triflation caused by excess Tf_2O,[30] the amount of Tf_2O was reduced to 1.5 equiv. In this case, isocyanate **32** was rapidly formed (within 20 min) as the only detectable reaction product and exhibited prolonged stability without conversion into dihydroisoquinolinones (entry 4). The identification of isocyanate **32** strengthened our belief that an *N*-Boc carbamate substrate could be transformed into a dihydroisoquinolinone via an isocyanate intermediate. The addition of excess Lewis acid (10 equiv) to the reaction mixture containing isocyanate **32** to facilitate the Friedel-Crafts reaction led to the formation of dihydroisoquinolinones **27** and **28** without the formation of the *N*-triflated derivatives (entries 5, 6, and 7). The yields from this stepwise process were much improved compared to that under the Banwell conditions (85–90% vs. 42%), although the degree of regioselectivity was slightly lower (8.5:1–9.7:1 vs. 12.2:1).

The above results implied that the reaction process was greatly influenced by the amount of base present and the acidity of the reaction medium. By further changing the molar ratios of Tf_2O and 2-chloropyridine, we finally determined the optimal reaction conditions for **25** to be 1.1 equiv of Tf_2O, 1.5 equiv of 2-chloropyridine and heating at 35 ^oC for 20 h. Under these conditions, *N*-triflation was minimized, and the product **27** was obtained in high yield and with high regioselectivity (entry 8).

Table 1. Optimization of Friedel-Crafts-type cyclization[a]



Entry	Tf_2O (eq)	Base (eq)	Lewis acid	*t* (h)	Yield (%)[b,c]	(**27**+**30**): (**28**+**31**)[d]
1	5.0	DMAP (3.0)	–	20	42	12.2:1
2	5.0	Py (3.0)	–	20	21+(45)	12.1:1
3	5.0	2-ClPy (3.0)	–	20	44+(40)	12.4:1
4	1.5	2-ClPy (3.0)	–	20	–	–
5[e]	1.5	2-ClPy (3.0)	$BF_3{\cdot}Et_2O$	2	86	8.5:1
6[e]	1.5	2-ClPy (3.0)	MsOH	0.5	90	8.5:1
7[e]	1.5	2-ClPy (3.0)	TfOH	0.5	85	9.7:1
8[f]	1.1	2-ClPy (1.5)	–	20	82	12.3:1

[a]Reaction conditions: **25** (0.3 mmol), Tf_2O, base, CH_2Cl_2 (10 mL), 0 ºC for 0.5 h and then rt. [b]Isolated yield of the mixture of **27** and **28**. The values in parentheses are the isolated yield of the mixture of **30** and **31**. [c]Each regioisomer could be separated. [d]Determined by ^1H NMR analysis. [e]Lewis acid was added after the formation of isocyanate. [f]Reaction was conducted at –78 ºC for 0.5 h and then at 35 ºC for 20 h.

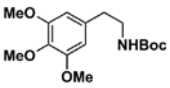
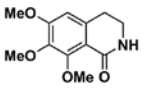
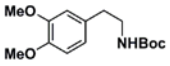
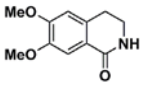
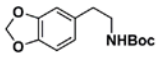
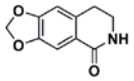
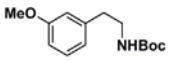
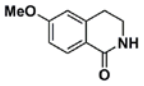
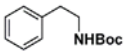
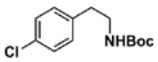
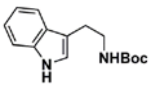
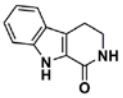
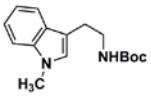
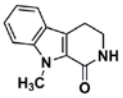
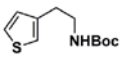
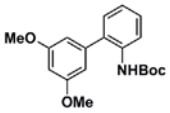
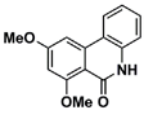
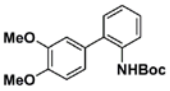
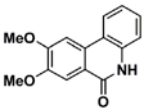
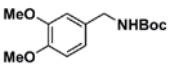
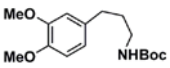
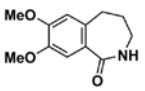
Using the optimized reaction conditions with or without an acid additive, we next investigated the scope of substrates (Table 2). All substrates were first subjected to the reaction conditions without an acid additive (Method A: Tf_2O (1.1 equiv), 2-ClPy (1.5 equiv), –78 ºC to rt). If method A gave unsatisfactory results, the Lewis acid was added

after the formation of isocyanate to facilitate the Friedel-Crafts reaction (Method B: Tf_2O (1.1 equiv), 2-ClPy (1.5 equiv), then $BF_3 \cdot Et_2O$ (5.0 equiv), –78 ºC to rt). The results are summarized in Table 2. Remarkably, the cyclizations of all compounds bearing electron-rich aryl rings proceeded in high yield and with high or exclusive regioselectivity.

The *N*-Boc carbamate **33a** bearing a trimethoxy-substituted benzene ring as a nucleophilic moiety was easily transformed to 3,4-dihydroisoquinolin-1-one **34a** using method A in 71% yield (entry 1). The 3,4-dimethoxy substituted substrate **33b** also afforded the cyclized product **34b** in high yield (87%) using method A with very high regioselectivity (>20:1) (entry 2). However, substrates **33c** and **33d** required the addition of $BF_3 \cdot Et_2O$ for cyclization (entries 3 and 4) to give products. High yield and regioselectivity were also observed. The Lewis acid requirement for these substrates might be due to the lower nucleophilicity of their aryl ring moieties compared to that of the electron-rich substrates **33a** and **33b**.[31] Substrates with electron-deficient or neutral groups at the aryl moiety did not undergo the cyclization reaction under either set of reaction conditions, yielding only the corresponding isocyanates (entries 5 and 6).

The phenyl rings could also be replaced by heteroarene units. Electron-rich heterocycles, such as indole and *N*-methyl indole moieties, showed good cyclization efficiency to afford tetrahyrdo-*β*-carbolin-1-ones **34g** and **34h** in good yield (70% and 92%, respectively) (entries 7 and 8). With the aid of an acid additive, thiopen substrate **33i** also produced the cyclized product **34i** in 79% yield (entry 9).

Table 2. Substrate Scope of the Reactions

Entry	*N*-Boc carbamate (**33**)		Product (**34**)		Method[a]	Yield[b] (%)
1	**33a**		**34a**		A	71
2	**33b**		**34b**		A	87
3	**33c**		**34c**		B	86
4	**33d**		**34d**		B	83[c]
5	**33e**		**34e**	-	A or B	-[d]
6	**33f**		**34f**	-	A or B	-[d]
7	**33g**		**34g**		A	70
8	**33h**		**34h**		A	92
9	**33i**		**34i**		B	79
10	**33j**		**34j**		A	81
11	**33k**		**34k**		B	70
12	**33l**		**34l**	-	A or B	-[d]
13	**33m**		**34m**		B	83[e]

[a]Method A: Tf_2O (1.1 equiv), 2-ClPy (1.5 equiv), CH_2Cl_2, –78 ºC to rt. Method B: Tf_2O (1.1 equiv), 2-ClPy

(1.5 equiv), $BF_3 \cdot Et_2O$ (5.0 equiv), CH_2Cl_2, –78 ºC to rt. [b]Isolated yield. [c]Regioisomeric mixture (18:1). [d]Lactam product was not detected. [e]TfOH was used instead of $BF_3 \cdot Et_2O$.

The substrate for which the *N*-Boc carbamate group is bonded directly to an aromatic ring also provided the cyclized product (entries 10 and 11). The 3,5-dimethoxy substituted substrate **33j** smoothly afforded phenanthridone **34j** in high yield (81%) under method A. However, the 3,4-dimethoxy substituted substrate **33k** required the addition of the Lewis acid for cyclization and provided phenanthridone **34k** in a slightly lower yield (70%).

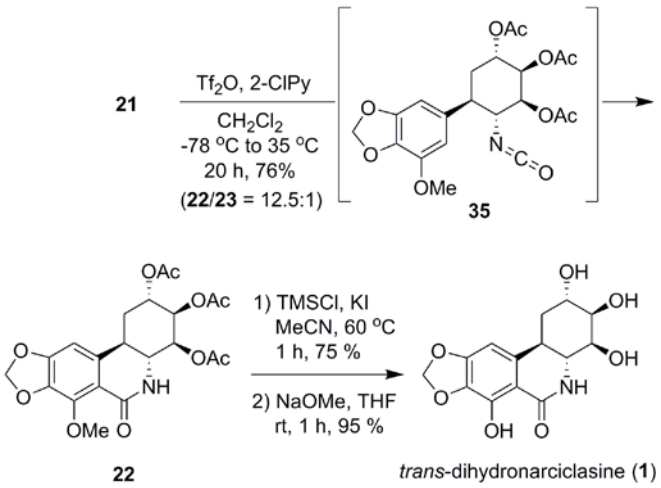
We also explored the feasibility of forming a five- or seven-membered ring lactam using these methods. Attempts to generate the dihydro-isoindolone **34l**, from the reaction of substrate **33l** under the above conditions produced complicated unidentified mixtures (entry 12).[32] However, under acid-induced conditions, *γ*-arylpropylcarbamate **33m** could be transformed into the benzo[*c*]azepin-1-one **34m** in 83% yield (entry 13).

II-6. Final Stages and Completion of the Synthesis

By applying these optimized conditions to *N*–Boc carbamate **21**, we were able to obtain the desired cyclization product **22** with very high regioselectivity (12.5:1) in 76% yield (Scheme 6). After careful monitoring of the reaction of **21**, we could identify a somewhat unstable isocyanate intermediate **35** and its identity was mainly confirmed by IR

spectroscopy (2253 cm^{-1}). The total synthesis was completed by demethylation with TMSCl/KI (75%) and removal of the acetate protecting groups with NaOMe (95%) to give (+)–**1**. The spectroscopic and optical rotation data of the synthetic material were in good agreement with those reported for the natural product.

Scheme 6. Completion of the total synthesis.



III. Conclusion

In conclusion, the total synthesis of (+)-*trans*-dihydronarciclasine (**1**) has been accomplished in 16% overall yield in a completely substrate-controlled manner from the readily accessible chiral starting material **9**. One of the unique features of this synthesis is the highly stereocontrolled introduction of the five contiguous stereogenic centers based on a single stereocenter in starting material. Two of the five stereocenters were defined by an Ireland-Claisen rearrangement, and the other three centers were created through diastereoselective reduction and oxidation reactions. The stereoselectivity for introducing all of the stereogenic reactions was excellent, with only a single diastereomer of each product being observed. The concise nature of this total synthesis hinges in part on the first demonstration of the successful conversion of a Claisen rearrangement product into a six-membered cyclic vinylogous ester via a regioselective Wacker oxidation and Dieckmann condensation based sequence. The successful B-ring formation with high regioselectivity from an *N*-Boc substrate via an isocyanate intermediate is also quite noteworthy, and the present transformation is a useful complement to Banwell's variant of the Bischler-Napieralski reaction in the synthesis of dihydroisocarbostyrils from *β*-arylethylcarbamates.

IV. Experimental

IV-1. General.

All chemicals were of reagent grade and used as received. All reactions were performed under an inert atmosphere of dry nitrogen using distilled dry solvents. Reactions were monitored by TLC analysis using silica gel 60 F-254 thin layer chromatography plates. Flash column chromatography was carried out on silica gel (230-400 mesh). Optical rotations were measured using sodium light (D line 589.3 nm). ^{1}H NMR (300, 400 or 500 MHz) and ^{13}C NMR (75, 100 or 125 MHz) spectra were recorded in δ units relative to the non-deuterated solvent as the internal reference. IR spectra were measured on a Fourier Transform Infrared spectrometer. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB).

IV-2. Experimental procedure and spectroscopic data analysis

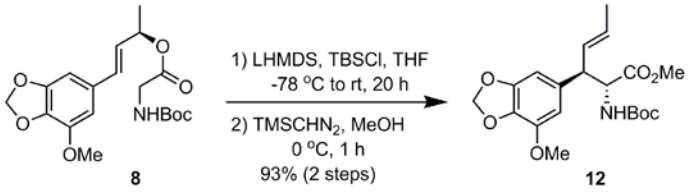
IV-2.1. All the compounds of the total synthesis process

(*R*,*E*)-4-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)but-3-en-2-yl 2-(*tert*-butoxycarbonyl amino)ace tate (8):

To a solution of allylic alcohol **9**[9] (3.50 g, 15.75 mmol, 1.0 equiv) in CH_2Cl_2 (80 mL) were added *N*-Boc-glycine (3.31 g, 18.90 mmol, 1.2 equiv), DMAP (383 mg, 3.15 mmol, 0.2 equiv), and DCC (3.90 g, 18.90 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred for 2 h at room temperature followed by dilution with hexane. The generated white precipitate was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give allylic amino acid ester **8** (5.91 g, 99%) as a pale yellow oil. $[\alpha]^{25}_{D}$ +84.7 (*c* = 2.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.5 Hz, 3H), 1.40 (s, 9H), 3.85 (s, 3H), 3.85−3.86 (m, 2H), 5.09 (br s, 1H), 5.50 (pent, *J* = 6.5 Hz, 1H), 5.90 (s, 2H), 5.96 (dd, *J* = 6.9, 15.8 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.48 (s, 1H), 6.55 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.25, 28.16 (3C), 42.56, 56.39, 72.15, 79.76, 99.99, 101.43, 106.90, 126.72, 130.91, 131.87, 135.18,

143.43, 149.02, 155.61, 169.57 ppm; IR ($CHCl_3$): υ_{max} = 3399, 2979, 1713, 1627, 1510, 1431, 1368 cm^{-1}; MS (FAB): *m/z*: 379 $[M]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{25}NO_7$: 379.1631 $[M]^+$; found: 379.1630.

(2*R*,3*R*,*E*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)hex-4-enoate (12):



To a stirred solution of ester **8** (5.00 g, 13.18 mmol, 1.0 equiv) in THF (80 mL) was added TBSCl (5.96 g, 39.54 mmol, 3.0 equiv) in THF (8 mL). After the mixture was cooled to –78 °C, LHMDS (1.0 m soln. in THF, 40 mL, 39.54 mmol, 3.0 equiv) was slowly added to the reaction flask over 30 min. The reaction mixture was slowly warmed to room temperature and stirred for 20 h. The reaction was quenched with saturated NH_4Cl solution at 0 °C, stirred for another 1 h at room temperature, and then the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the desired acid **12-acid** as a single isomer, which was used in the next step without further purification. A small amount of pure acid was isolated by column chromatography on silica gel (hexane/EtOAc, 2:1 + 1% AcOH) for ^1H NMR and HRMS analysis. ^1H NMR (400 MHz, CD_3OD): δ = 1.33 (s, 9H), 1.65 (d, *J* = 5.9 Hz, 3H), 3.52 (t, *J* = 8.6 Hz, 1H), 3.85 (s, 3H),

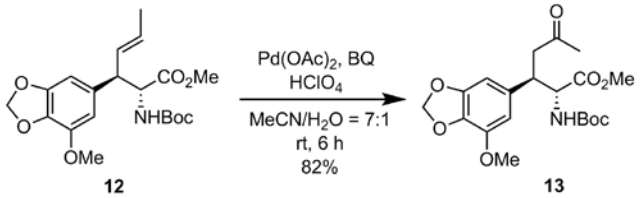
4.34 (d, *J* = 8.8 Hz, 1H), 5.50−5.58 (m, 1H), 5.60−5.67 (m, 1H), 5.86 (d, *J* = 3.4 Hz, 2H), 6.42 (s, 1H), 6.44 ppm (s, 1H); MS (FAB): *m/z*: 402 $[M+23]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{25}NO_7$: 379.1631 $[M]^+$; found: 379.1655.

The crude mixture obtained above was dissolved in MeOH (44 mL), and trimethylsilyl-diazomethane solution (2.0 m soln. in diethyl ether, 17 mL, 32.95 mmol, 2.5 equiv) was added dropwise, causing instantaneous bubbling, along with a change from colorless to yellow. After allowing the reaction to proceed for 1 h, the reaction was quenched with small amount of acetic acid, at which time gas evolved and the reaction mixture became colorless. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1) to give the desired ester **12** (4.82 g, 93% for 2 steps) as a pale yellow solid. $[\alpha]^{25}_D$ −45.2 (*c* = 0.88, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 9H), 1.67 (d, *J* = 5.1 Hz, 3H), 3.54−3.50 (m, 1H), 3.66 (s, 3H), 3.87 (s, 3H), 4.50 (t, *J* = 7.3 Hz, 1H), 4.78 (d, *J* = 7.6 Hz, 1H), 5.54−5.63 (m, 2H), 5.92 (s, 2H), 6.31 (s, 1H), 6.36 ppm (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.81, 28.02 (3C), 51.16, 51.71, 56.44, 57.76, 79.77, 101.23, 101.80, 107.36, 128.24, 128.87, 133.95, 134.10, 143.38, 148.88, 155.07, 172.02 ppm; IR ($CHCl_3$): υ_{max} = 3377, 2976, 1744, 1715, 1634, 1510, 1452 cm^{-1}; MS (FAB): *m/z*: 394 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{28}NO_7$: 394.1866 $[M+H]^+$; found: 394.1972.

The diastereomeric purity of ester **12** was determined by crude ^{1}H NMR spectrum analysis. The enantiomeric purity of ester **12** (>99%*ee*) was determined by chiral HPLC analysis (CHIRALCEL OJ-H, 2-propanol/hexane (0 to 10%, 60 min), flow rate: 0.5

mL/min, t_R: (chiral sample) = 37.7 min [(–)-isomer]; t_R (racemic sample) = 37.1 [(–)-isomer], 42.5 min [(+)-isomer], detected at 225 nm).

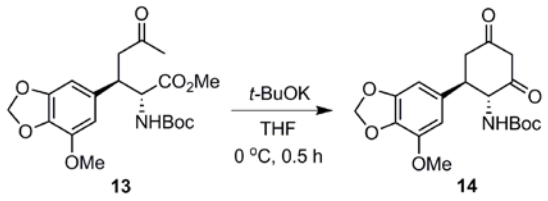
(2*R*,3*R*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-5-oxohexanoate (13):



To a mixture of $Pd(OAc)_2$ (685 mg, 3.05 mmol, 0.3 equiv) and 1,4-benzoquinone (1.10 g, 10.17 mmol, 1.0 equiv) in MeCN/H_2O (7:1, v/v, 51 mL) was added $HClO_4$ (1.0 m soln. in MeCN, 2.0 mL, 2.03 mmol, 0.2 equiv). The resulting solution was stirred 1 h at room temperature and ester **12** (4.00 g, 10.17 mmol, 1.0 equiv) was added to reaction flask. After being stirred for 6 h at room temperature, the reaction was quenched with saturated $NaHCO_3$ solution at 0 °C and then the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Due to similar R_f values for the hydroquinone generated and the product under various eluent conditions, hydroquinone was acetylated under standard conditions (Ac_2O, NEt_3, DMAP, CH_2Cl_2). The resulting crude mixture was purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1) to give desired methyl ketone **13** (3.41 g, 82%) as a pale brown oil. $[\alpha]^{25}_D$ −55.3 (*c* = 0.72, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 2.13 (s, 3H), 2.67 (dd, *J* = 5.4, 17.7 Hz, 1H), 2.98 (dd, *J* = 8.4, 17.8 Hz,

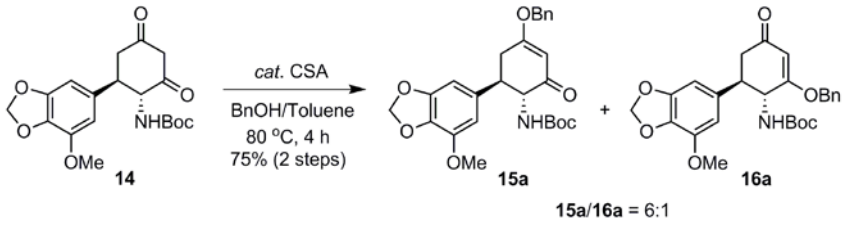
1H), 3.70 (s, 3H), 3.78 (br s, 1H), 3.86 (s, 3H), 4.60 (d, J = 5.0 Hz, 1H), 4.97 (d, J = 8.3 Hz, 1H), 5.92 (s, 2H), 6.26 (d, J = 1.3 Hz, 1H), 6.31 ppm (d, J = 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.14 (3C), 30.14, 42.25, 45.14, 52.10, 56.47, 56.58, 79.96, 101.31, 101.64, 108.10, 133.00, 134.46, 143.30, 148.94, 155.70, 171.40, 205.80 ppm; IR ($CHCl_3$): υ_{max} = 3381, 2978, 1714, 1633, 1510, 1452, 1435 cm^{-1}; MS (FAB): *m/z*: 409 $[M]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{27}NO_8$: 409.1737 $[M]^+$; found: 409.1749.

***tert*-butyl (1*R*,2*R*)-2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-4,6-dioxocyclohexyl carbamate (14):**



To a stirred solution of methyl ketone **13** (3.00 g, 7.33 mmol, 1.0 equiv) in THF (40 mL) was slowly added *t*-BuOK (1.0 m soln. in THF, 19 mL, 18.3 mmol, 2.5 equiv) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, then quenched by addition of saturated NH_4Cl solution, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give β-diketone **14**.[12] The resulting white solid was used in the next step without further purification.

Vinylogous benzyl ester (15a and 16a):



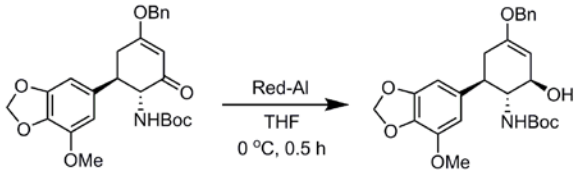
To a mixture of crude *β*-diketone **14** in toluene (30 mL) and benzyl alcohol (7.5 mL), catalytic 10-camphorsulfonic acid (170 mg, 0.73 mmol, 0.1 equiv) was added. The reaction mixture was stirred for 4 h at 80 °C and then quenched by the addition of NEt_3 (0.1 mL) at 0 °C. This was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give vinylogous benzyl ester **15a** (2.19 g, 64%) and minor isomer **16a** (377 mg, 11%) as white solids. The minor isomer **16a** could be cleanly separated chromatographically and be isomerized back to the 6:1 mixture (combined 70% yield) in favor of **15a** by resubjection to the above etherification conditions. Additional **15a** (226 mg) could be obtained from **16a** through this isomerization.

***Major isomer 15a* (*tert*-butyl (1*R*,6*R*)-4-(benzyloxy)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2-oxocyclohex-3-enylcarbamate):** $[\alpha]^{25}_{D}$ +21.6 (*c* = 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 2.66 (dd, *J* = 4.7, 17.5 Hz, 1H), 2.81−2.89 (m, 1H), 3.21 (t, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 4.25−4.38 (m, 1H), 4.75−4.90 (m, 3H), 5.55 (s, 1H), 5.87 (d, *J* = 2.3 Hz, 2H), 6.42 (s, 1H), 6.45 (s, 1H), 7.29−7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.01 (3C), 37.65, 45.95, 56.41, 59.58, 70.86, 79.30, 101.20,

101.70, 101.88, 107.20, 127.63 (2C), 128.48, 128.59 (2C), 134.11, 134.54, 134.59, 143.30, 148.65, 155.73, 174.82, 194.95 ppm; IR ($CHCl_3$): υ_{max} = 2977, 1708, 1665, 1608, 1514, 1453, 1364 cm^{-1}; MS (FAB): *m/z*: 468 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{26}H_{30}NO_7$: 468.2022 $[M+H]^+$; found: 468.2010.

***Minor isomer 16a* (*tert*-butyl (1*R*,6*R*)-2-(benzyloxy)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-4-oxocyclohex-2-enylcarbamate):** ^1H NMR (500 MHz, DMSO-d_6): δ = 1.25 (s, 9H), 2.36 (dd, *J* = 3.9, 16.1 Hz, 1H), 2.78 (dd, *J* = 13.4, 16.0 Hz, 1H), 3.29−3.39 (m, 1H), 3.80 (s, 3H), 4.66 (t, *J* = 9.9 Hz, 1H), 4.97−5.03 (m, 2H), 5.50 (s, 1H), 5.94 (s, 2H), 6.59 (s, 2H), 7.04 (d, *J* = 9.1 Hz, 1H), 7.33−7.39 ppm (m, 5H).

***tert*-butyl (1*R*,2*R*,6*R*)-4-(benzyloxy)-2-hydroxy-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)cyclohex-3-enylcarbamate (17):**

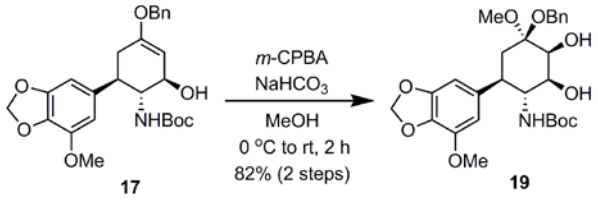


15a **17**

To a stirred solution of vinylogous benzyl ester **15a** (2.00 g, 4.28 mmol, 1.0 equiv) in THF (43 mL) was slowly added Red-Al (sodium bis(2-methoxyethoxy)aluminum dihydride (70% in toluene, ca. 3.6 m), 1.8 mL, 6.42 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred for additional 30 min, and then quenched by the addition of saturated NH_4Cl solution at 0 °C, and extracted twice with EtOAc. The combined organic

layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give allylic alcohol **17** as a single isomer.[33] Due to its instability under acidic conditions, the resulting pale yellow oil was used in the next step without further purification. The diastereomeric purity of alcohol **17** was determined by crude ^{1}H NMR spectrum analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 2.40 (dd, *J* = 5.1, 16.8 Hz, 1H), 2.52 (t, *J* = 16.8 Hz, 1H), 2.89 (dt, *J* = 5.5, 11.5 Hz, 1H), 3.69 (td, *J* = 7.1, 11.8 Hz, 1H), 3.89 (s, 3H), 4.41 (br s, 2H), 4.67−4.90 (m, 3H), 5.90−6.00 (m, 2H), 6.38−6.44 (m, 2H), 7.27−7.42 ppm (m, 5H).

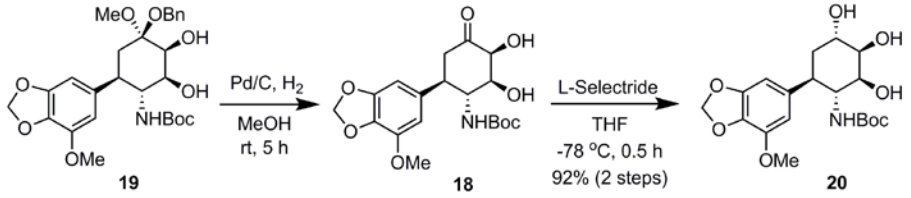
***tert*-butyl (1*R*,2*S*,3*S*,4*R*,6*R*)-4-(benzyloxy)-2,3-dihydroxy-4-methoxy-6-(7-methoxy benzo[*d*][1,3]dioxol-5-yl)cyclohexylcarbamate (19):**



To the crude mixture of allylic alcohol **17** obtained in the previous step in MeOH (22 mL) was added $NaHCO_3$ (1.08 g, 12.84 mmol, 3.0 equiv) and *m*-CPBA (1.11 g, 6.42 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, and then quenched by addition of saturated $Na_2S_2O_3$ solution at 0 °C, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:2) to give ketal **19** (1.82 g, 82% for 2 steps from **15a**) as a

single isomer. $[\alpha]^{25}_{D}$ +11.8 (*c* = 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O): δ = 1.29 (s, 9H), 2.02 (dd, *J* = 2.0, 13.9 Hz, 1H), 2.12 (t, *J* = 13.9 Hz, 1H), 2.51 (dt, *J* = 3.5, 12.5 Hz, 1H), 3.27 (s, 3H), 3.73 (dd, *J* = 2.5, 9.8 Hz, 1H), 3.86 (s, 3H), 3.91 (br s, 1H), 4.13 (s, 1H), 4.38 (d, *J* = 7.9 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 5.90 (d, *J* = 3.2 Hz, 2H), 6.40 (d, *J* = 3.8 Hz, 2H), 7.26−7.38 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.07 (3C), 34.95, 43.21, 47.81, 54.94, 56.46, 62.33, 70.87, 73.64, 79.77, 100.99, 101.19, 101.97, 106.77, 127.33, 127.42 (2C), 128.26 (2C), 133.89, 135.89, 138.08, 143.49, 148.71, 157.19 ppm; IR ($CHCl_3$): υ_{max} = 3398, 2973, 1691, 1635, 1515 cm^{-1}; MS (FAB): *m/z*: 518 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{27}H_{36}NO_9$: 518.2390 $[M+H]^+$; found: 518.2377.

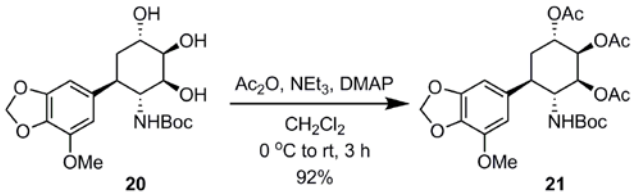
***tert*-butyl (1*R*,2*S*,3*R*,4*S*,6*R*)-2,3,4-trihydroxy-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)cyclohexylcarbamate (20):**



To a solution of **19** (1.50 g, 2.90 mol, 1.0 equiv) in MeOH (30 mL) was added 10% Pd/C (450 mg, 30% wt. of **19**). The flask was evacuated, filled with H_2, and stirred at room temperature for 5 h. After this, the reaction mixture was diluted with EtOAc, filtered through a pad of Celite, and concentrated in vacuo to give crude mixture of dihydroxyketone **18**. Due to its instability, resulting colorless oil was used in the next step

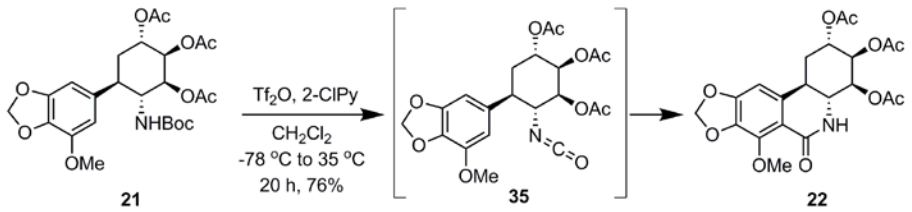
without further purification. To the crude mixture of **18** in THF (30 mL) was slowly added L-Selectride (lithium tri-*sec*-butylborohydride, 1.0 m soln. in THF, 4.4 mL, 4.35 mmol, 1.5 equiv) at −78 °C. The reaction mixture was stirred for 30 min at -78 °C, and then quenched by addition of saturated NH_4Cl solution at 0 °C, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/Acetone, 1:2) to give triol **20** (1.06 g, 92% for 2 steps from **19**) as a single isomer. $[\alpha]^{25}_D$ +0.99 (*c* = 0.65, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ = 1.25 (s, 9H), 1.71 (d, *J* = 13.6 Hz, 1H), 2.10 (t, *J* = 13.2 Hz, 1H), 2.86 (t, *J* = 11.0 Hz, 1H), 3.34 (s, 1H), 3.70−3.78 (m, 1H), 3.81 (s, 1H), 3.85 (s, 3H), 3.95 (s, 2H), 5.80−5.86 (m, 2H), 6.44 (s, 1H), 6.49 ppm (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 29.47 (3C), 37.08, 44.65, 56.77, 57.89, 71.52, 73.56, 75.01, 80.34, 102.95, 103.98, 109.91, 135.68, 139.56, 145.36, 150.76, 159.41 ppm; IR (neat): υ_{max} = 3388, 2925, 1683, 1635, 1513 cm^{-1}; MS (FAB): *m/z*: 397 $[M]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{27}NO_8$: 397.1737 $[M]^+$; found 397.1753.

(1*S*,2*R*,3*S*,4*R*,5*R*)-4-(*tert*-butoxycarbonylamino)-5-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)cyclohexane-1,2,3-triyl triacetate (21):



To a mixture of triol **20** (700 mg, 1.76 mmol, 1.0 equiv) in CH_2Cl_2 (18 mL) was added NEt_3 (2.0 mL, 14.08 mmol, 8.0 equiv), DMAP (21.5 mg, 0.176 mmol, 0.1 equiv), and Ac_2O (0.84 mL, 8.81 mmol, 5.0 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction was quenched by addition brine at 0 °C and then the mixture was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1) to give triacetate **21** (848 mg, 92%) as a colorless oil. $[\alpha]^{25}_D$ +44.4 (*c* = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (br s, 9H), 1.90−2.02 (m, 5H), 2.10 (s, 3H), 2.15 (s, 3H), 2.74−2.84 (m, 1H), 3.86 (s, 3H), 4.06−4.19 (m, 1H), 4.20−4.27 (m, 1H), 4.99 (d, *J* = 3.0 Hz, 1H), 5.13 (d, *J* = 9.8 Hz, 1H), 5.28 (s, 1H), 5.88 (d, *J* = 5.1 Hz, 2H), 6.36−6.42 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.69, 20.92, 21.01, 28.03 (3C), 33.76, 43.52, 52.12, 56.52, 68.83, 69.05, 71.17, 79.17, 101.27, 101.90, 107.02, 134.05, 135.01, 143.41, 148.81, 155.21, 169.20, 169.38, 170.53 ppm; IR ($CHCl_3$): υ_{max} = 3387, 2976, 1750, 1634, 1514 cm^{-1}; MS (FAB): *m/z*: 523 $[M]^+$; HRMS (FAB): *m/z* calcd for $C_{25}H_{33}NO_{11}$: 523.2054 $[M]^+$; found: 523.2070.

(2*S*,3*R*,4*S*,4a*R*,11b*R*)-7-methoxy-6-oxo-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo [4,5-*j*]phenanthridine-2,3,4-triyl triacetate (22):

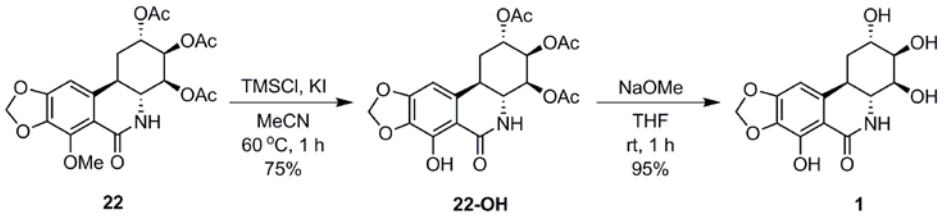


To a stirred solution of triacetate **21** (100 mg, 0.19 mmol, 1.0 equiv) in CH_2Cl_2 (9 mL) was added 2-chloropyridine (1.0 m soln. in CH_2Cl_2, 0.3 mL, 0.29 mmol, 1.5 equiv) and triflic anhydride (0.2 m soln. in CH_2Cl_2, 1.1. mL, 0.21 mmol, 1.1 equiv) at −78 °C. After stirring at −78 °C for 30 min, the reaction mixture was warmed to 35 °C and stirred for an additional 20 h. After that, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution at 0 °C. This was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/Acetone, 1:1) to give the major isomer **22** (65 mg, 76%) as a white solid along with the minor isomer **23** (5 mg, 6%). $[\alpha]^{25}_D$ +131.3 (*c* = 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64 (br s, 1H), 1.85 (dt, *J* = 2.8, 13.6 Hz, 1H), 2.05 (s, 6H), 2.12 (s, 3H), 2.38 (d, *J* = 14.4 Hz, 1H), 3.05 (dt, *J* = 3.8, 12.4 Hz, 1H), 3.64 (t, *J* = 11.6 Hz, 1H), 4.04 (s, 3H), 5.13 (d, *J* = 3.0 Hz, 1H), 5,16 (d, *J* = 3.0 Hz, 1H), 5.40 (t, *J* = 3.0 Hz, 1H), 5.98 (d, *J* = 7.8 Hz, 2H), 6.14 (br s, 1H), 6.44 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.68, 20.76, 21.02, 26.95, 35.94, 52.12, 60.81, 67.37, 68.57, 71.49, 98.98, 101.68, 115.51, 137.13, 137.41, 145.08, 152.06, 163.75, 169.13, 169.38, 170.37 ppm; IR ($CHCl_3$): υ_{max} = 3197, 2926, 1752, 1669, 1612 cm^{-1}; MS (FAB): *m/z*: 450 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{21}H_{24}NO_{10}$: 450.1400 $[M+H]^+$; found: 450.1409.

Characterization of isocyanate 35

During the above reaction sequence (in this case, 1.5 equiv of Tf_2O and 3.0 equiv of 2-ClPy were used), isocyanate **35** could be obtained by quenching the reaction mixture with aqueous $NaHCO_3$ solution, before raising the temperature. This was then diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by short flash chromatography on silica gel (hexane/EtOAc, 1:1) to give isocyanate **35**. Since the compound appeared to decompose during the chromatography, the yield was not checked. The identity of isocyanate was confirmed by IR spectroscopy (2253 cm^{-1}). IR ($CHCl_3$): υ_{max} = 3014, 2939, 2852, **2253**, 1752, 1634, 1514 cm^{-1}.

(+)-*trans*-dihydronarciclasine (1):



22 **22-OH** **1**

To a stirred solution of lactam **22** (50.0 mg, 0.11 mmol, 1.0 equiv) in MeCN (5 mL) was added KI (18.4 mg, 0.11 mmol, 1.0 equiv) and TMSCl (0.5 m soln. in MeCN, 0.3 mL, 0.14 mmol, 1.3 equiv). The reaction mixture was stirred for 1 h at 60 °C and quenched by the addition of H_2O at 0 °C. This was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1) to give **22-OH** (36.2 mg, 75%) as a

white solid. $[\alpha]^{25}_{D}$ +81.8 (*c* = 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (dt, *J* = 2.7, 13.5 Hz, 1H), 2.07 (s, 6H), 2.12 (s, 3H), 2.41 (d, *J* = 14.5 Hz, 1H), 3.12 (dt, *J* = 3.6, 12.6 Hz, 1H), 3.76 (dd, *J* = 11.0, 12.7 Hz, 1H), 5.14−5.20 (m, 2H), 5.42 (t, *J* = 3.0 Hz, 1H), 5.98 (br s, 1H), 6.02 (d, *J* = 4.1 Hz, 2H), 6.31 (s, 1H), 12.29 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.70, 20.78, 21.03, 26.67, 34.55, 52.75, 67.23, 68.43, 71.62, 96.71, 102.33, 106.94, 133.18, 135.78, 146.47, 152.95, 169.15, 169.33, 170.13 ppm (2C); IR ($CHCl_3$): υ_{max} = 3335, 2924, 1752, 1673, 1627 cm^{-1}; MS (FAB): *m/z*: 436 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{22}NO_{10}$: 436.1244 $[M+H]^+$; found: 436.1245.

To a solution of **22-OH** (30.0 mg, 0.07 mmol, 1.0 equiv) in THF (7 mL) was added NaOMe (1.0 m soln. in MeOH, 0.7 mL, 10.0 equiv). After being stirred at room temperature for 1 h, the reaction was quenched by the addition of saturated NH_4Cl solution, and extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 10:1) to give (+)-*trans*-dihydronarciclasine **1** (20.3 mg, 95%) as a white solid. $[\alpha]^{25}_{D}$ +4.0 (*c* = 0.16, THF), (Literature.[4b] $[\alpha]^{25}_{D}$ +4.1 (*c* = 0.22, THF)); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.78−1.87 (m, 1H), 2.17−2.25 (m, 1H), 2.99 (dt, *J* = 3.4, 12.6 Hz, 1H), 3.46 (dd, *J* = 10.1, 13.0 Hz, 1H), 3.85 (dd, *J* = 3.0, 10.1 Hz, 1H), 3.90 (t, *J* = 2.9 Hz, 1H), 4.04−4.09 (m, 1H), 5.99 (d, *J* = 2.4 Hz, 2H), 6.44 ppm (s, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ = 30.43, 36.06, 57.17, 71.35, 72.33, 74.14, 98.47, 104.22, 109.05, 134.72, 140.53, 148.06, 155.10, 172.70 ppm; IR (neat): υ_{max} =

3354, 2923, 1625 cm^{-1}; MS (FAB): *m/z*: 310 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{14}H_{16}NO_7$: 310.0927 $[M+H]^+$; found: 310.0928.

IV-2.2. All the compounds of the Model studies and optimization process

IV-2.2.1. Representative procedure for preparation of *N*-Boc carbamate

***tert*-Butyl (2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (25)**:

NEt_3 (2.9 mL, 20.5 mmol, 2.0 equiv), DMAP (125 mg, 1.03 mmol, 0.1 equiv), and $(Boc)_2O$ (2.5 g, 11.3 mmol, 1.1 equiv) were added to a solution of 2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethanamine[34] (2.0 g, 10.3 mmol, 1.0 equiv) in CH_2Cl_2 (52 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by the addition of brine at 0 °C. The mixture was then extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give *N*-Boc carbamate **25** (2.8 g, 93%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9H), 2.66 (t, J = 6.9 Hz, 2H), 3.23−3.33 (m, 2H), 3.85 (s, 3H), 4.57 (br s, 1H), 5.89 (s, 2H), 6.31 (s, 1H), 6.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.36 (3C), 36.22, 41.87, 56.48, 79.22, 101.26, 102.75, 107.83, 133.44, 133.67, 143.52, 148.86, 155.80; IR ($CHCl_3$): υ_{max} = 3404, 3360, 2974, 2936, 1709, 1510 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{15}H_{22}NO_5$: 296.3389 $[M+H]^+$; found: 296.3396.

The amines required for the preparation of carbamate compounds **33a**-**33g**, **33i**, **33l**, and **33m** are commercially available. Carbamate **33h** were prepared from **33g** by simple *N*-methylation. The amines required for **33j** and **33k** were prepared by a previously developed procedure.[35]

***tert*-Butyl 3,4,5-trimethoxyphenethylcarbamate** (**33a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.72 (t, *J* = 6.9 Hz, 2H), 3.30−3.39 (m, 2H), 3.81 (s, 3H), 3.83 (s, 6H), 4.54 (br s, 1H), 6.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.37 (3C), 36.54, 41.72, 56.03 (2C), 60.78, 79.21, 105.62 (2C), 134.62, 136.50, 153.21 (2C), 155.82; IR ($CHCl_3$): υ_{max} = 3371, 2974, 2937, 1711 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{16}H_{26}NO_5$: 312.1811 [*M*+H]$^+$; found: 312.1820.

***tert*-Butyl 3,4-dimethoxyphenethylcarbamate** (**33b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 2.71 (t, *J* = 7.1 Hz, 2H), 3.28−3.35 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.51 (br s, 1H), 6.65−6.80 (m, 3H); HRMS (FAB): *m/z* calcd for $C_{15}H_{24}NO_4$: 282.1705 [*M*+H]$^+$; found: 282.1709.

***tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate** (**33c**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.69 (t, *J* = 7.0 Hz, 2H), 3.27−3.35 (m, 2H), 4.51 (br s, 1H), 5.91 (s, 2H), 6.60−6.66 (m, 2H), 6.72 (d, *J* = 7.9 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{14}H_{20}NO_4$: 266.1392 [*M*+H]$^+$; found: 266.1395.

***tert*-Butyl 3-methoxyphenethylcarbamate** (**33d**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.75 (t, J = 7.0 Hz, 2H), 3.33−3.37 (m, 2H), 3.78 (s, 3H), 4.52 (br s, 1H), 6.72−6.77 (m, 3H), 7.20 (t, J = 7.8 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{14}H_{22}NO_3$: 252.1600 [M+H]$^+$; found: 252.1603.

***tert*-Butyl phenethylcarbamate** (**33e**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 2.83 (t, J = 7.3 Hz, 2H), 3.35−3.45 (m, 2H), 4.57 (br s, 1H), 7.16−7.38 (m, 5H); HRMS (FAB): *m/z* calcd for $C_{13}H_{20}NO_2$: 222.1494 [M+H]$^+$; found: 222.1490.

***tert*-Butyl 4-chlorophenethylcarbamate** (**33f**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 2.74 (t, J = 6.9 Hz, 2H), 3.23−3.36 (m, 2H), 4.50 (br s, 1H), 7.07−7.13 (m, 2H), 7.23−7.27 (m, 2H); HRMS (FAB): *m/z* calcd for $C_{13}H_{19}ClNO_2$: 256.1104 [M+H]$^+$; found: 256.1109.

***tert*-Butyl (2-(1*H*-indol-3-yl)ethyl)carbamate** (**33g**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.94 (t, J = 6.8 Hz, 2H), 3.38−3.51 (m, 2H), 4.60 (br s, 1H), 6.98−7.13 (m, 1H), 7.10 (dt, J = 1.0, 7.4 Hz, 1H), 7.19 (dt, J = 1.2, 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 8.07 (br s, 1H); HRMS (FAB): *m/z* calcd for $C_{15}H_{21}N_2O_2$: 261.1603 [M+H]$^+$; found: 261.1608.

***tert*-Butyl (2-(1-methyl-1*H*-indol-3-yl)ethyl)carbamate** (**33h**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.93 (t, *J* = 6.8 Hz, 2H), 3.42 (br s, 2H), 3.74 (s, 3H), 4.57 (br s, 1H), 6.87 (s, 1H), 7.07−7.11 (m, 1H), 7.19−7.30 (m, 2H), 7.57 (d, *J* = 7.7 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{16}H_{23}N_2O_2$: 275.1760 $[M+H]^+$; found: 275.1765.

***tert*-Butyl (2-(thiophen-3-yl)ethyl)carbamate** (**33i**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.80 (t, *J* = 6.9 Hz, 2H), 3.30−3.41 (m, 2H), 4.54 (br s, 1H), 6.92−6.98 (m, 2H), 7.25−7.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.35 (3C), 30.65, 40.99, 79.21, 121.25, 125.75, 128.05, 139.23, 155.80; IR ($CHCl_3$): υ_{max} = 3350, 2977, 2931, 1694 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{11}H_{18}NO_2S$: 228.1058 $[M+H]^+$; found: 228.1063.

***tert*-Butyl (3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)carbamate** (**33j**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 3.80 (s, 6H), 6.48 (s, 3H), 6.60 (br s, 1H), 7.06 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.20 (dd, *J* = 1.7, 7.5 Hz, 1H) 7.32 (dt, *J* = 1.7, 8.4 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{19}H_{24}NO_4$: 330.1705 $[M+H]^+$; found: 330.1709.

***tert*-Butyl (3',4'-dimethoxy-[1,1'-biphenyl]-2-yl)carbamate** (**33k**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 3.88 (s, 3H), 3.93 (s, 3H), 6.54 (br s, 1H), 6.85−6.98 (m, 3H), 7.06 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.20 (dd, *J* = 1.7, 7.5 Hz, 1H) 7.30 (dt, *J* = 1.4, 7.1 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.30 (3C), 55.88, 55.91,

80.40, 111.51, 112.30, 119.55, 121.46, 122.87, 128.15, 130.05, 130.70, 130.97, 135.34, 148.53, 149.09, 152.84; IR ($CHCl_3$): υ_{max} = 3345, 2977, 2934, 1730 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{19}H_{24}NO_4$: 330.1705 [*M*+H]$^+$; found: 330.1704.

***tert*-Butyl 3,4-dimethoxybenzylcarbamate** (**33l**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 3.84 (s, 6H), 4.21 (d, *J* = 5.3 Hz, 2H), 4.79 (br s, 1H), 6.74−6.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.31 (3C), 44.42, 55.72, 55.83, 79.27, 110.79, 111.09, 119.55, 131.56, 148.20, 148.99, 155.77; IR ($CHCl_3$): υ_{max} = 3352, 2975, 2934, 1725 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{14}H_{22}NO_4$: 268.1549 [*M*+H]$^+$; found: 268.1553.

***tert*-Butyl (3-(3,4-dimethoxyphenyl)propyl)carbamate** (**33m**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 1.77 (quintet, *J* = 7.4 Hz, 2H), 2.57 (t, *J* = 7.8 Hz, 2H), 3.05−3.20 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.50 (br s, 1H), 6.68−6.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.39 (3C), 31.92, 32.68, 40.19, 55.81, 55.92, 79.11, 111.31, 111.74, 120.13, 134.19, 147.27, 148.89, 155.95; IR ($CHCl_3$): υ_{max} = 3374, 2974, 2935, 1709 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{16}H_{26}NO_4$: 296.1862 [*M*+H]$^+$; found: 296.1862.

IV-2.2.2. Methyl (2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (**26**):

NEt_3 (2.9 mL, 20.5 mmol, 2.0 equiv), DMAP (125 mg, 1.03 mmol, 0.1 equiv), and methyl chloroformate (0.9 mL, 11.3 mmol, 1.1 equiv) were added to a solution of 2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethanamine[34] (2.0 g, 10.3 mmol, 1.0 equiv) in CH_2Cl_2

(52 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by the addition of brine at 0 °C. The mixture was then extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give methyl carbamate **26** (2.5 g, 95%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (t, J = 6.8 Hz, 2H), 3.33−3.42 (m, 2H), 3.64 (s, 3H), 3.86 (s, 3H), 4.69 (br s, 1H), 5.91 (s, 2H), 6.31 (s, 1H), 6.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.18, 42.28, 52.03, 56.53, 101.29, 102.64, 107.90, 133.19, 133.75, 143.56, 148.93, 156.91; IR ($CHCl_3$): υ_{max} = 3340, 2942, 2890, 2843, 1697 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{12}H_{16}NO_5$: 254.1028 $[M+H]^+$; found: 254.1025.

IV-2.2.3. General procedure for the Friedel-Crafts-type cyclization associated with Table 1

The specified amount of base (DMAP, pyridine, or 2-chloropyridine) and triflic anhydride (1.0 M soln. in CH_2Cl_2) was added to a stirred solution of *N*-Boc carbamate **25** (89 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at the specified temperature (0 ºC or -78 ºC). After 30 min, the reaction mixture was warmed to room temperature and stirred for the indicated duration. (In the case of entries 5, 6, and 7 of Table 1, Lewis acid was added after 20 min, stirred another 10 min and then warm to room temperature.) Then, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution at 0 ºC.

This solution was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to give the cyclized products **27** and **28** as a white solid. (When DMAP was replaced by the less basic pyridine or 2-chloropyridine (Table 1, entries 2 and 3), *N*-triflated derivatives **30** and **31** were also generated.) Isocyanate **32** could be obtained by quenching the reaction mixture with aqueous $NaHCO_3$ solution before the addition of Lewis acid.

4-Methoxy-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (**27**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.79 (t, J = 6.4 Hz, 2H), 3.37 (dt, J = 3.6, 6.3 Hz, 2H), 4.03 (s, 3H), 5.94 (s, 2H), 6.38 (s, 1H), 6.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.38, 39.69, 60.76, 101.37, 102.29, 115.68, 134.50, 137.04, 144.74, 151.26, 164.68; IR ($CHCl_3$): υ_{max} = 3406, 3221, 2929, 1664 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{11}H_{12}NO_4$: 222.0766 [M+H]$^+$; found: 222.0761.

4-Methoxy-7,8-dihydro-[1,3]dioxolo[4,5-*h*]isoquinolin-9(6*H*)-one (**28**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (t, J = 6.4 Hz, 2H), 3.47 (dt, J = 2.9, 6.4 Hz, 2H), 3.91 (s, 3H), 6.10 (s, 2H), 6.33 (s, 1H), 6.44 (br s, 1H); IR ($CHCl_3$): υ_{max} = 3179, 2991, 2903, 1657, 1636 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{11}H_{12}NO_4$: 222.0766 [M+H]$^+$; found: 222.0768.

4-Methoxy-6-((trifluoromethyl)sulfonyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (**30**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97 (t, J = 6.0 Hz, 2H), 4.03 (t, J = 5.9 Hz, 2H), 4.05 (s, 3H), 6.01 (s, 2H), 6.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.22, 46.45, 60.64, 102.09, 102.29, 117.43, 121.72, 137.26, 137.51, 146.04, 153.72, 159.88; IR ($CHCl_3$): υ_{max} = 3008, 2956, 2905, 1700, 1608 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{12}H_{11}F_3NO_6S$: 354.0259 $[M+H]^+$; found: 354.0268.

4-Methoxy-8-((trifluoromethyl)sulfonyl)-7,8-dihydro-[1,3]dioxolo[4,5-*h*]isoquinolin-9(6*H*)-one (**31**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.05 (t, J = 5.9 Hz, 2H), 3.96 (s, 3H), 4.11 (t, J = 6.1 Hz, 2H), 6.14 (s, 2H), 6.36 (s, 1H); IR ($CHCl_3$): υ_{max} = 3010, 2981, 2911, 1678, 1603 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{12}H_{11}F_3NO_6S$: 354.0259 $[M+H]^+$; found: 354.0265.

6-(2-Isocyanatoethyl)-4-methoxybenzo[*d*][1,3]dioxole (**32**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.79 (t, J = 6.8 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 3.88 (s, 3H), 5.96 (s, 2H), 6.36 (d, J = 1.5 Hz, 1H), 6.38 (d, J = 1.6 Hz,, 1H); IR ($CHCl_3$): υ_{max} = 2943, 2892, 2274, 1634, 1512 (cm^{-1}).

IV-2.2.4. Final optimized procedure for the Friedel-Crafts-type cyclization utilized in Table 2

Method A : 2-Chloropyridine (0.45 mmol, 1.5 equiv) and triflic anhydride (0.33 mmol, 1.1 equiv) were added to a stirred solution of *N*-Boc carbamate **33** (0.30 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) at -78 ºC. After 30 min, the reaction mixture was warmed to room temperature and stirred for 20 h. Next, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution at 0 ºC, diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. This residue was purified by column chromatography on silica gel using an appropriate CH_2Cl_2/MeOH mixture as the eluent to yield the cyclized product **34**.

Method B : Identical to method A except for the addition of $BF_3 \cdot Et_2O$ 20 min after the addition of Tf_2O. In this case, the reaction was completed within 2 h.

6,7,8-Trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**34a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (t, *J* = 6.3 Hz, 2H), 3.40−3.44 (m, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 6.01 (br s, 1H), 6.48 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{12}H_{16}NO_4$: 238.1079 $[M+H]^+$; found: 238.1083.

6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**34b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.91 (t, *J* = 6.8 Hz, 2H), 3.53 (dt, *J* = 2.8, 6.4 Hz, 2H), 3.91 (s, 6H), 6.01 (br s, 1H), 6.65 (s, 1H), 7.55 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{11}H_{14}NO_3$: 208.0974 $[M+H]^+$; found: 208.0979.

7,8-Dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (**34c**): ^{1}H NMR (300 MHz $CDCl_3$): δ = 2.86 (t, *J* = 6.6 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 5.97 (s, 2H), 6.62 (s, 1H), 6.80 (br s, 1H), 7.47 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{10}H_{10}NO_3$: 192.0661 $[M+H]^+$; found: 192.0657.

6-Methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**34d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.94 (t, *J* = 6.5 Hz, 2H), 3.52 (dt, *J* = 2.7, 6.5 Hz, 2H), 3.83 (s, 3H), 6.11 (br s, 1H), 6.68 (s, 1H), 6.83 (dd, *J* = 2.1, 8.6 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{10}H_{12}NO_2$: 178.0868 $[M+H]^+$; found: 178.0873.

2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (**34g**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.05 (t, *J* = 7.0 Hz, 2H), 3.71 (dt, *J* = 2.0, 6.9 Hz, 2H), 6.25 (br s, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 9.96 (br s, 1H); HRMS (FAB): *m/z* calcd for $C_{11}H_{11}N_2O$: 187.0871 $[M+H]^+$; found: 187.0876.

9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (**34h**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.04 (t, *J* = 6.9 Hz, 2H), 3.64 (dt, *J* = 2.7, 6.8 Hz, 2H), 4.10 (s, 3H), 5.57 (br s, 1H), 7.14 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.32−7.38 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{12}H_{13}N_2O$: 201.1028 $[M+H]^+$; found: 201.1025.

5,6-Dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one (**34i**): ^{1}H NMR (400 MHz, $CDCl_3$): δ =

2.90 (t, *J* = 6.9 Hz, 2H), 3.60 (dt, *J* = 2.2, 6.8 Hz, 2H), 6.48 (br s, 1H), 6.92 (d, *J* = 4.8 Hz, 1H), 7.47 (d, *J* = 4.8 Hz, 1H); HRMS (FAB): *m/z* calcd for C_7H_8NOS: 154.0327 $[M+H]^+$; found: 154.0328.

7,9-dimethoxyphenanthridin-6(5*H*)-one (**34j**): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3H), 3.97 (s, 3H), 6.70 (d, *J* = 1.7 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.41−7.48 (m, 2H), 8.32 (d, *J* = 8.1 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{15}H_{14}NO_3$: 256.0974 $[M+H]^+$; found: 256.0979.

8,9-dimethoxyphenanthridin-6(5*H*)-one (**34k**): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.90 (s, 3H), 4.02 (s, 3H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.88 (s, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 11.56 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{15}H_{14}NO_3$: 256.0974 $[M+H]^+$; found: 256.0978.

7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (**34m**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (quintet, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 7.1 Hz, 2H), 3.12 (q, *J* = 6.4 Hz, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 6.22 (br s, 1H), 6.65 (s, 1H), 7.24 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{12}H_{16}NO_3$: 222.1130 $[M+H]^+$; found: 222.1134.

IV-3. Analysis of molecular geometries of 15 and 16

***Theoretical Calculations*:** Theoretical calculations of regioisomers **15b (A)** and **16b (B)** were performed using the DMol^3 module in Material Studio 5.5^{TM}. The two regioisomers were optimized by the density functional theory (DFT) at the DNP level. A generalized gradient approximation (GAA) for the exchange correlation function of Perdew, Burke, and Ernzerhof (PBE) was used with the double-numerical plus polarization (DNP) as implemented in DMol^3.

The computational energy minimization using DMol^3 program suggests that product **15b** is thermodynamically more stable than other conformer **16b**, which is consistent with the experimental result. The calculated energy difference between **15b** and **16b** is about 1.3586 kcal/mol.

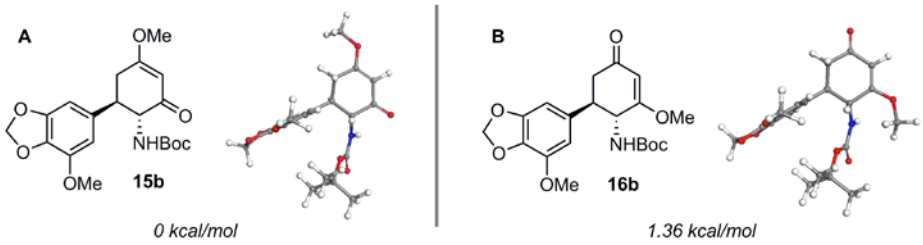


Figure 1. Density functional calculations at the PBE/DNP level on **15b** and **16b**.

Compound	*Hartree (Ha)*	*kcal/mol*	*Relative energy (kcal/mol)*
15b	-1.357390686 x 10^3	-851775.403 x 10^5	0
16b	-1.357388521 x 10^3	-851774.0444 x 10^5	1.358621

1Ha = 627.509391 kcal/mol

$\triangle G = -RTlnK$ (R = 0.001987 kcal K^{-1} mol^{-1}, T= 293.15 K)

lnK = (-1.358621 kcal/mol) / (-0.001987 kcal K^{-1} mol^{-1} x 293.15 K) = 2.3324

$K = e^{2.3324} = 10.303$

***Calculation input*:** All calculations are performed under following conditions.

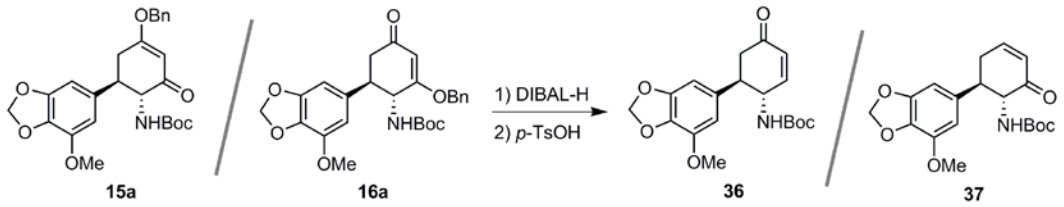
 # Task parameters

Calculate	optimize
Opt_energy_convergence	1.0000e–005
Opt_gradient_convergence	2.0000e–003 A
Opt_displacement_convergence	5.0000e–003 A
Opt_iterations	50
Opt_max_displacement	0.3000 A
Symmetry	0ff
Max_memory	4096

 # Electronic parameters

Spin_polarization	restricted
Charge	0
Basis	dnp
Pseudopotential	none
Functional	pbe
Aux_density	octupole
Integration_grid	fine
Occupation	fermi
Cutoff_Global	3.7000 angstrom
Scf_density_convergence	1.0000e–006
Scf_charge_mixing	0.2000
Scf_iterations	50
Scf_diis	6 pulay

***2D COSY NMR analysis of Enones*:** The chemical identities of **15a** and **16a** are also supported by the results of 2D COSY NMR experiments conducted on the corresponding enones **36** and **37**. Enones **36** and **37** were easily synthesized from vinylogous benzyl esters **15a** and **16a** by the well-known sequence (hydride reduction and acid hydrolysis) as shown below.[36]



***tert*-butyl (1*S*,6*R*)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-4-oxocyclohex-2-enylcarbamate (36):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9H), 2.61−2.75 (m, 2H), 3.11−3.25 (m, 1H), 3.88 (s, 3H), 4.56 (br s, 2H), 5.94 (s, 2H), 6.06 (d, J = 9.9 Hz, 1H), 6.36−6.48 (m, 2H), 6.92 ppm (d, J = 9.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.18 (3C), 44.96, 48.13, 56.68, 60.37, 80.16, 101.35, 101.49, 107.22, 129.22, 134.48, 134.50, 141.61, 149.17, 152.23, 155.13, 197,54 ppm; MS (FAB): *m/z*: 362 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{24}NO_6$: 362.1604 $[M+H]^+$; found: 362.1609.

***tert*-butyl (1*R*,6*R*)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2-oxocyclohex-3-enylcarbamate (37):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9H), 2.63−2.70 (m, 2H), 3.11−3.22 (m, 1H), 3.88 (s, 3H), 4.47−4.60 (m, 1H), 4.61−4.72 (m, 1H), 5.92 (dd, J = 1.2, 4.6 Hz, 2H), 6.14 (d, J = 10.2, Hz, 1H), 6.43−6.49 (m, 2H), 6.95 ppm (td, J = 3.7, 9.7 Hz,

1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.14 (3C), 35.74, 48.29, 56.58, 60.49, 79.66, 101.38, 101.90, 127.27, 128.76, 134.27, 134.88, 143.46, 148.40, 148.81, 155.76, 196.66 ppm; MS (FAB): *m/z*: 362 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{24}NO_6$: 362.1604 $[M+H]^+$; found: 362.1607.

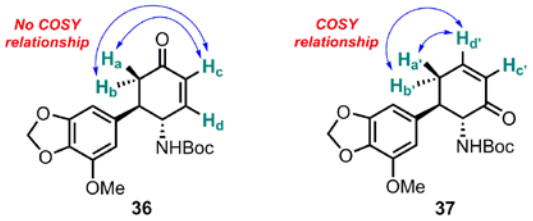


Figure 2. Rationale for using COSY relationships to distinguish between enones **36** and **37**.

V. References

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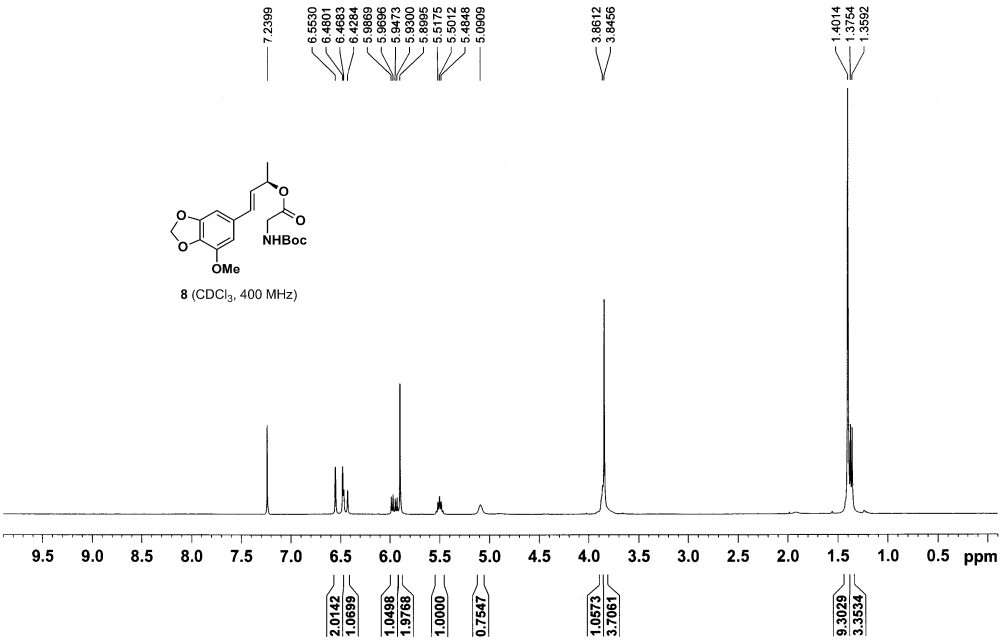
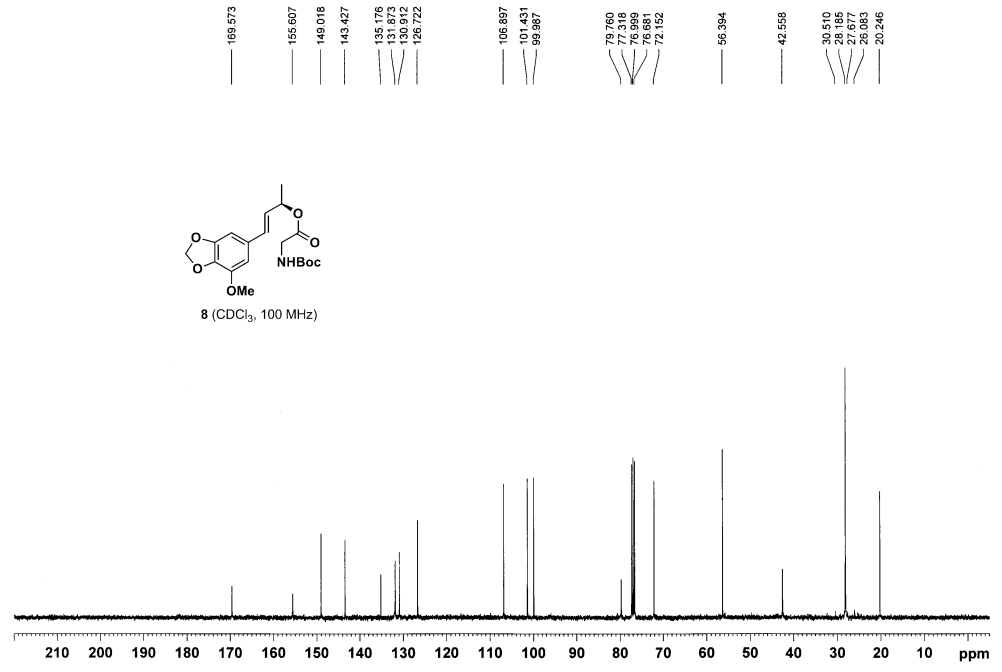
Appendix I.

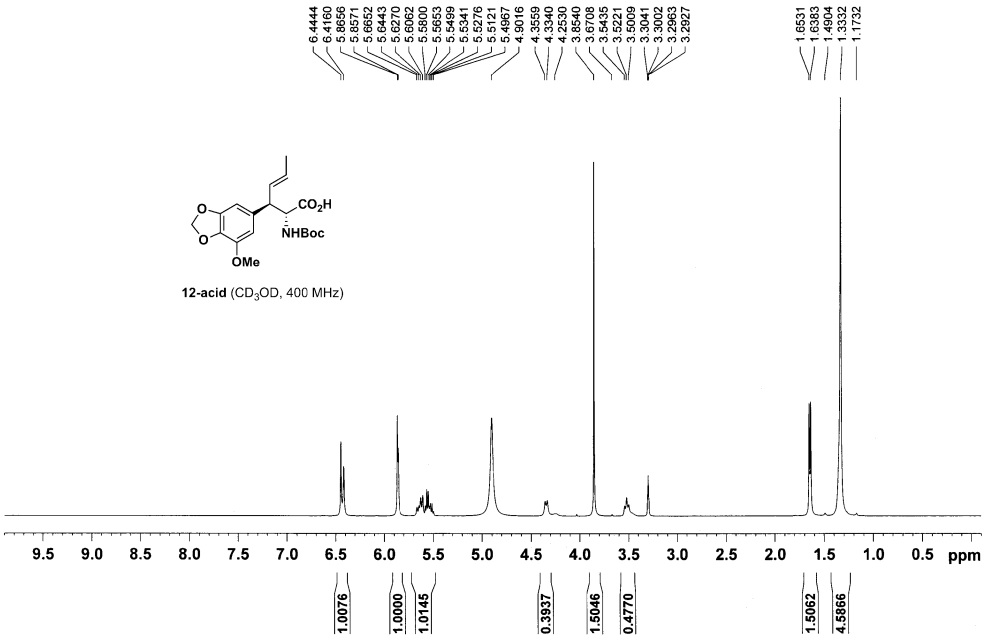
Spectra of Compounds.

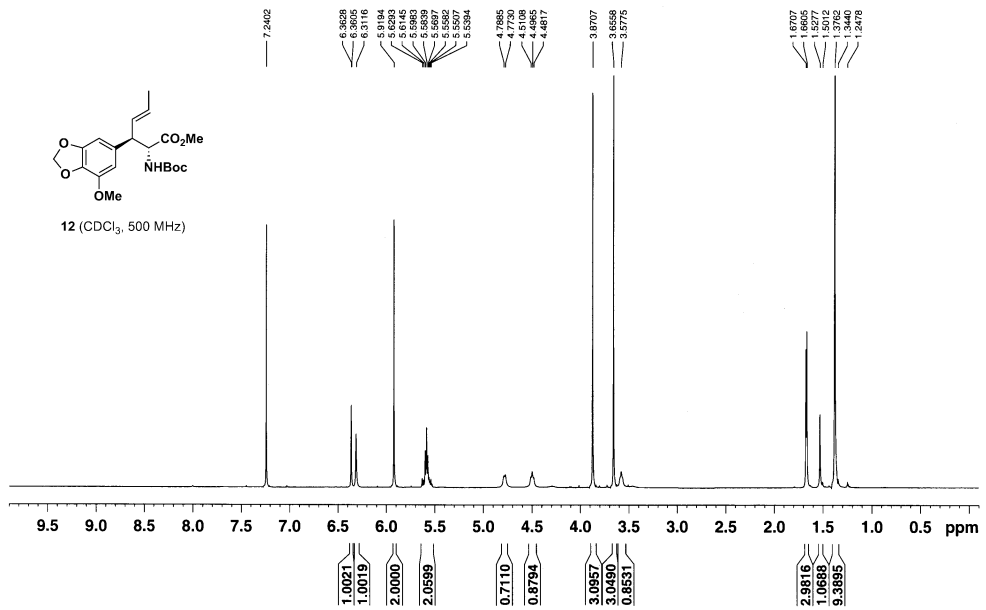
- ^{1}H & ^{13}C NMR spectrum of compound **8**



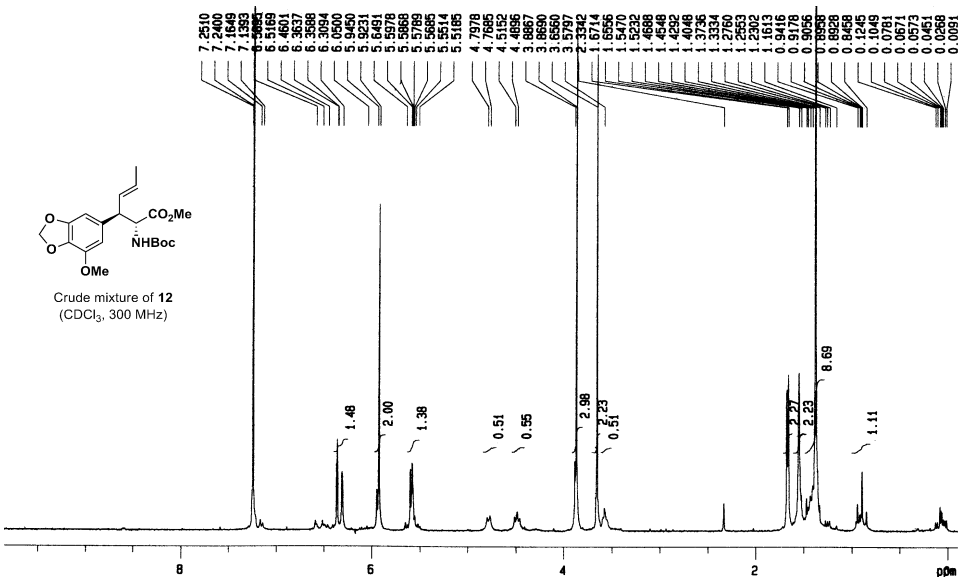


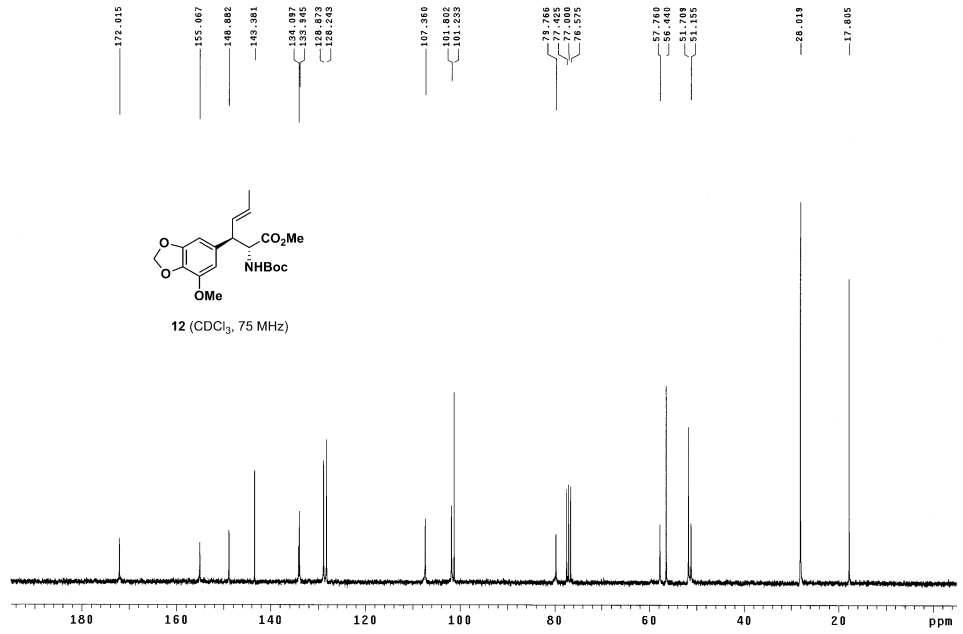
- ^{1}H NMR spectrum of compound **12-acid** & **12**





- Crude ^{1}H NMR spectrum of compound **12** & ^{13}C NMR spectrum of compound **12**



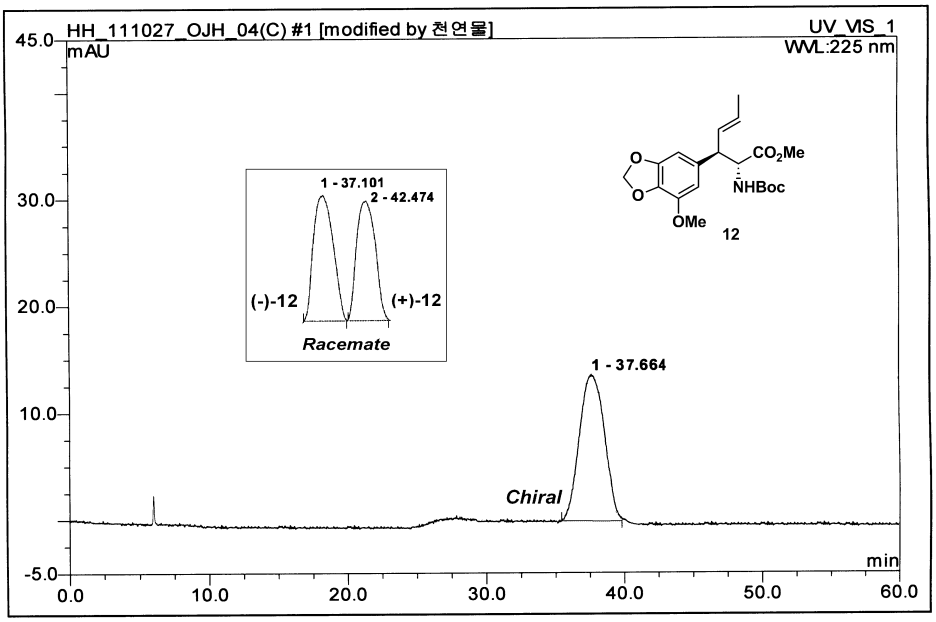


- Chiral HPLC spectrum of compound **12**

2011-10-28 4:48 PM

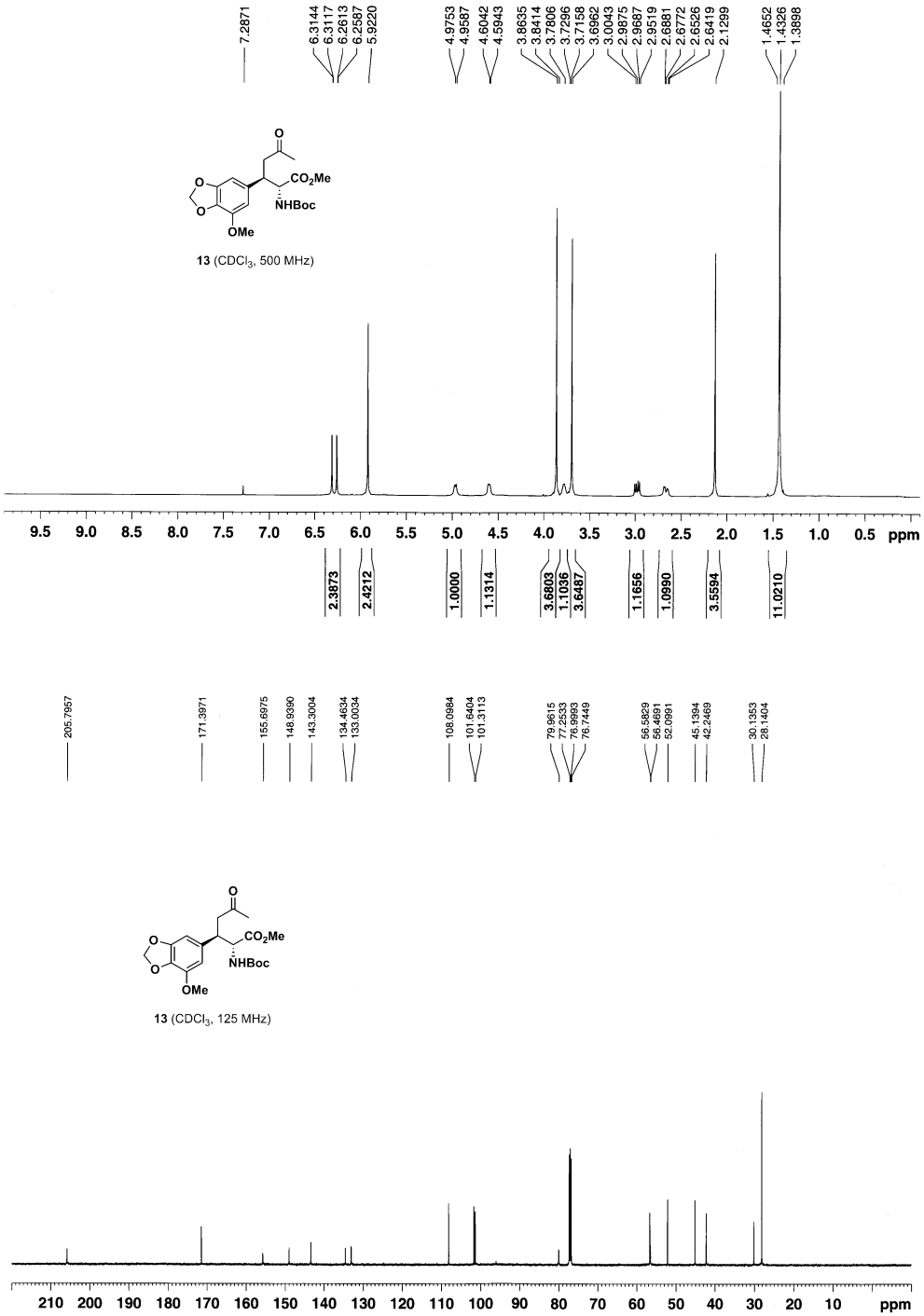
1 HH_111027_OJH_04

Sample Name:	**HH_111027_OJH_04**	*Injection Volume:*	**10.0**
Vial Number:	**RA2**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**HH_Gradient_0 to 10_05ml_60min**	*Bandwidth:*	**1**
Quantif. Method:	**HH_Gradient_0 to 10_05ml_60min**	*Dilution Factor:*	**1.0000**
Recording Time:	**2011-10-27 21:55**	*Sample Weight:*	**1.0000**
Run Time (min):	**60.00**	*Sample Amount:*	**1.0000**

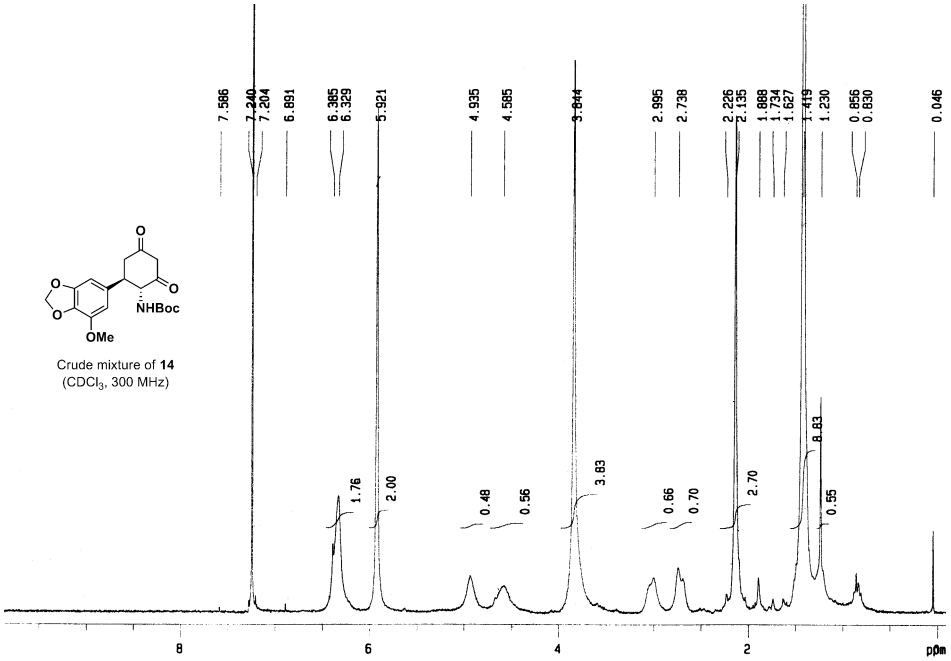


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	37.66	n.a.	13.718	34.546	100.00	n.a.	BM *
Total:			13.718	34.546	100.00	0.000	

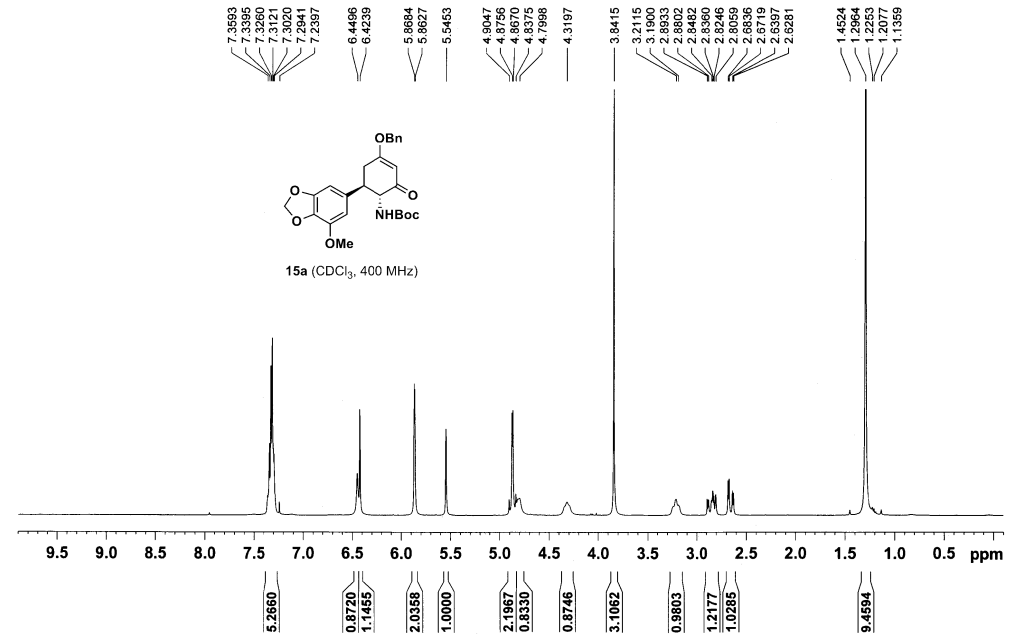
- ^{1}H & ^{13}C NMR spectrum of compound **13**

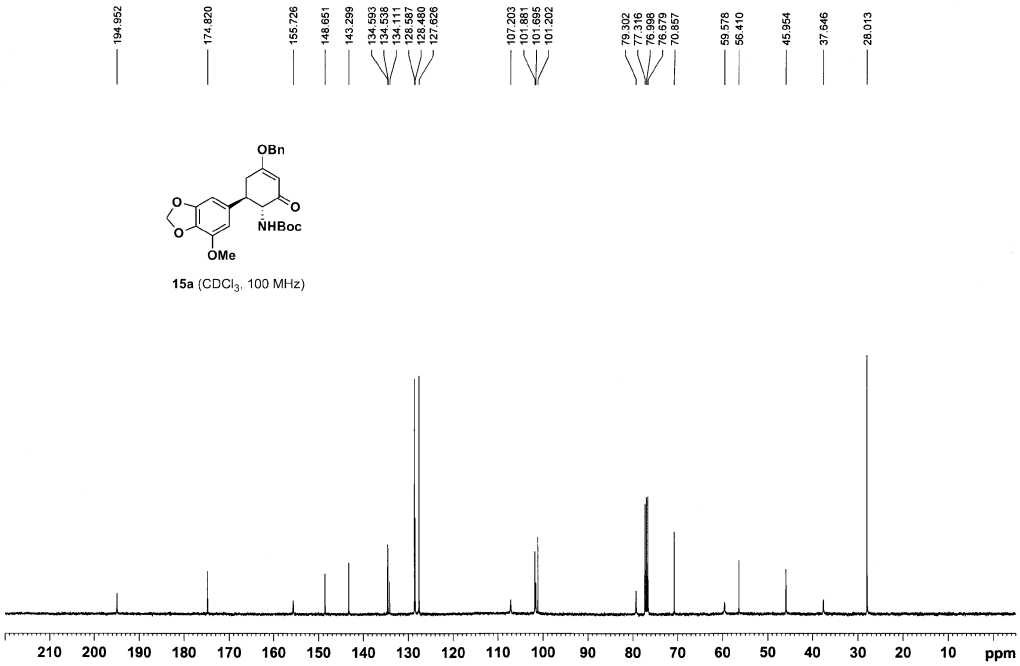


- Crude ^{1}H NMR spectrum of compound **14**

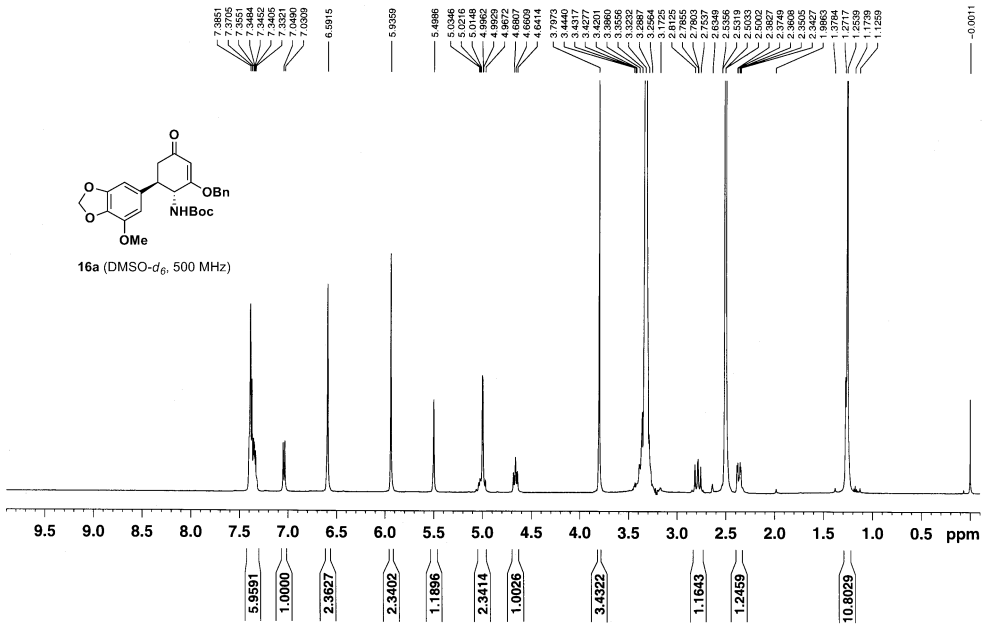


- ^{1}H & ^{13}C NMR spectrum of compound **15a**

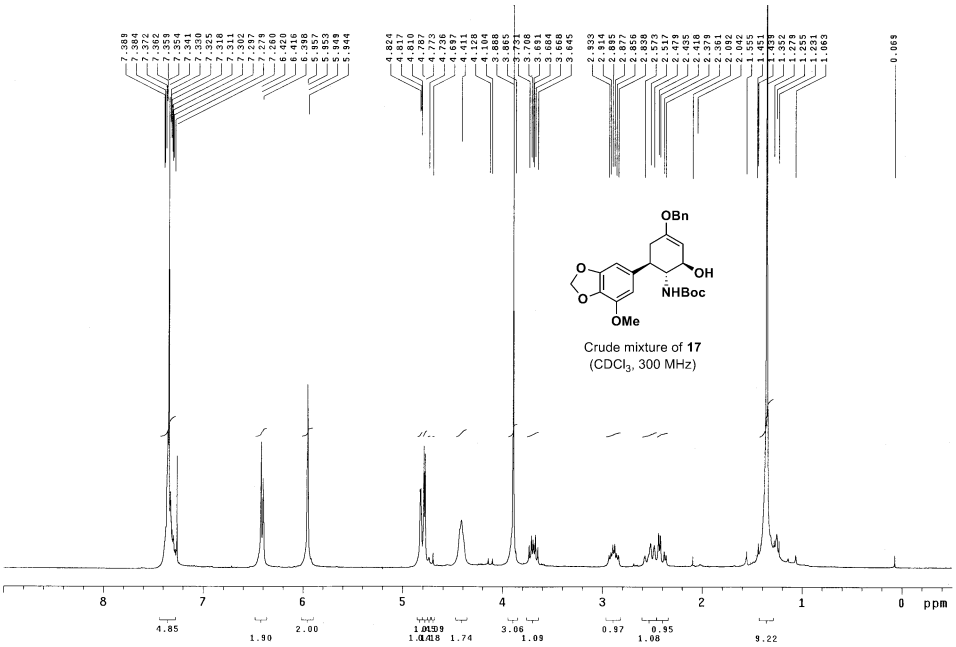


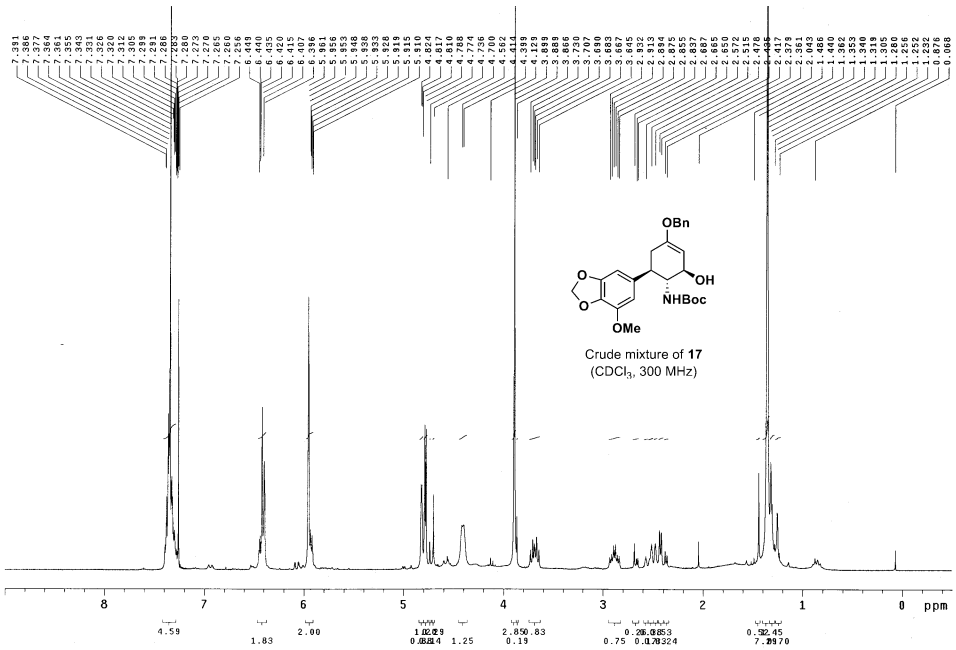


- ^{1}H NMR spectrum of compound **16a**

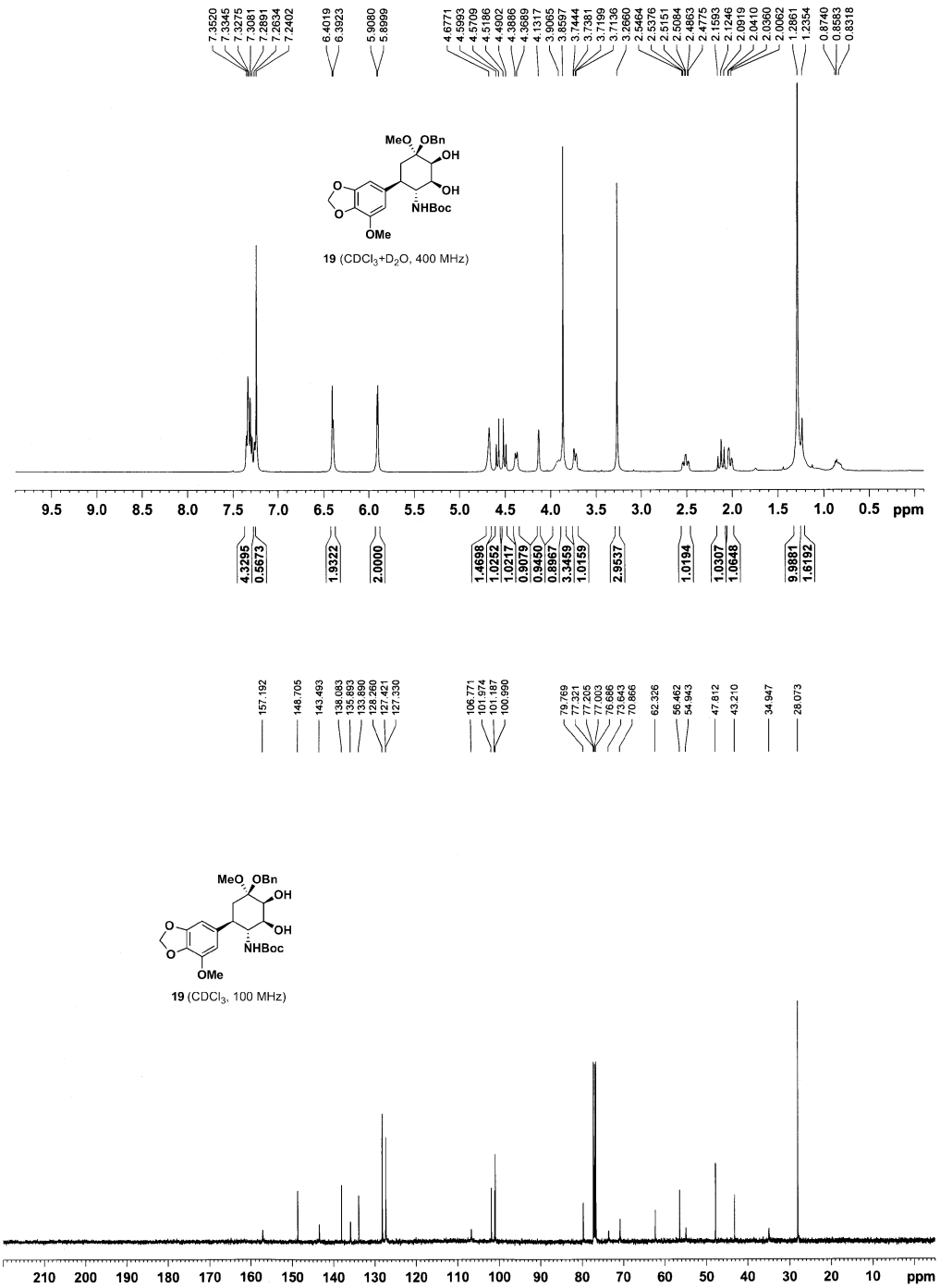


- Crude ^{1}H NMR spectrum of compound **17** (Red-Al (up) and LAH (down) reduction)

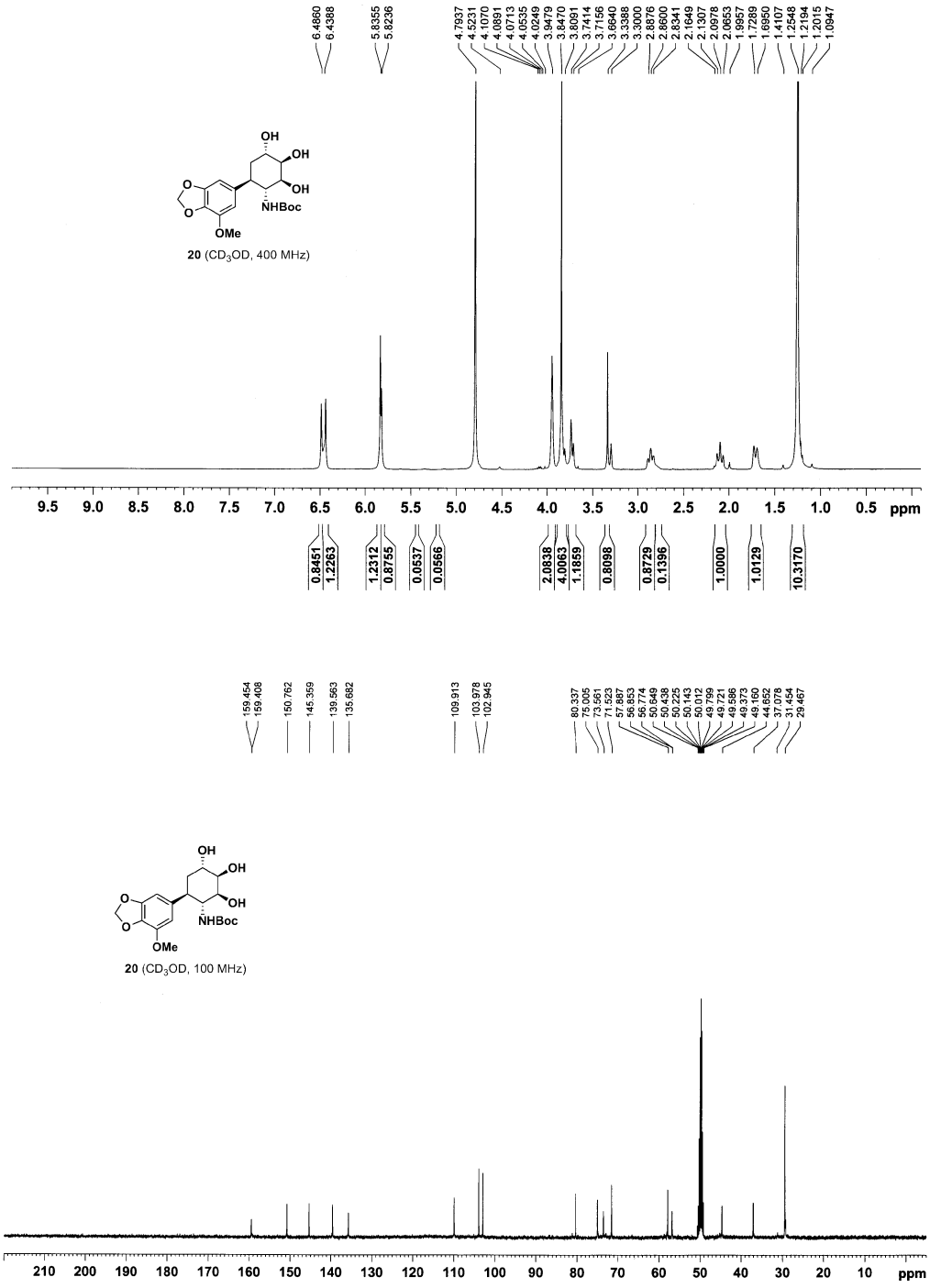




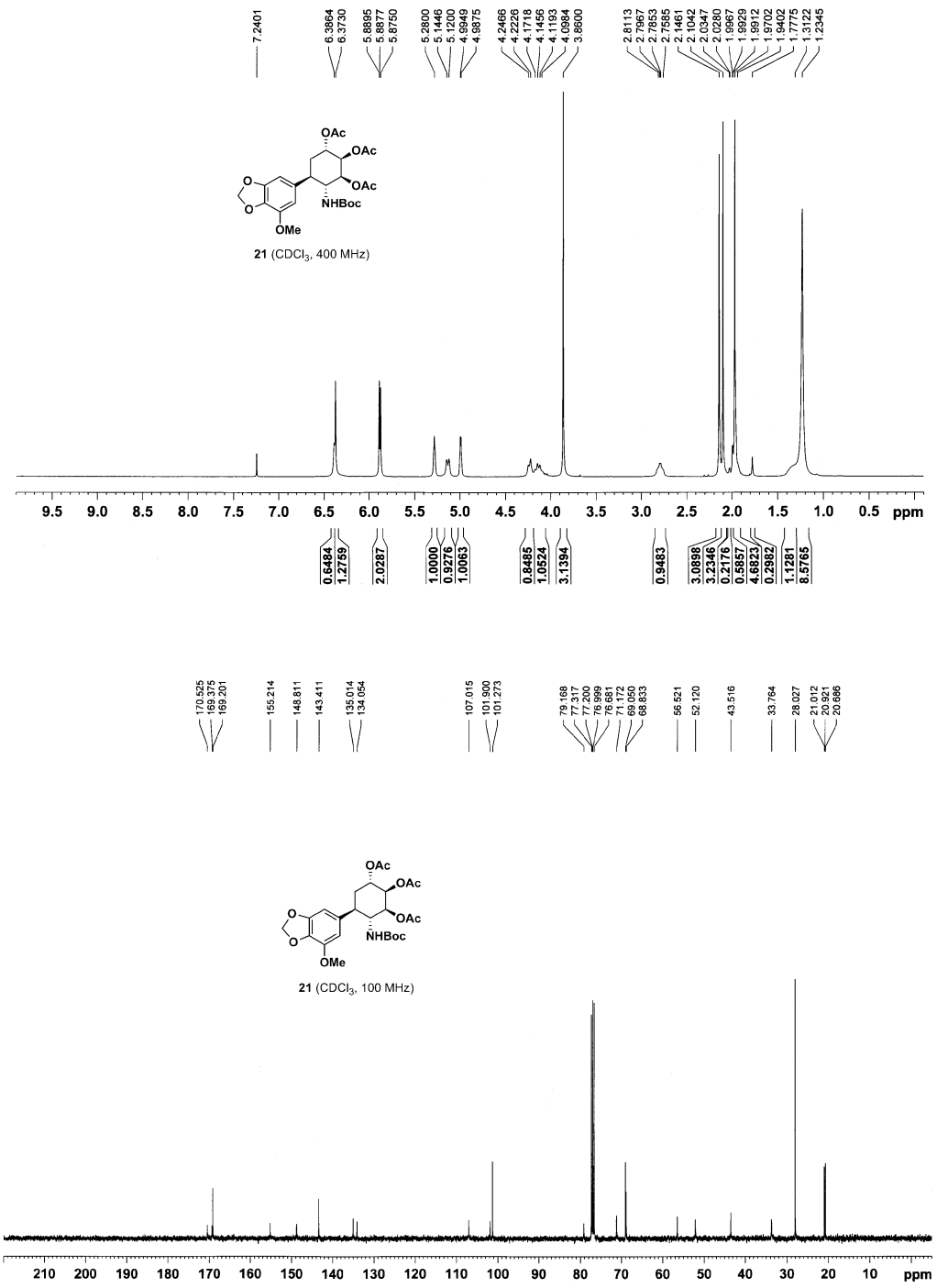
- ^{1}H & ^{13}C NMR spectrum of compound **19**



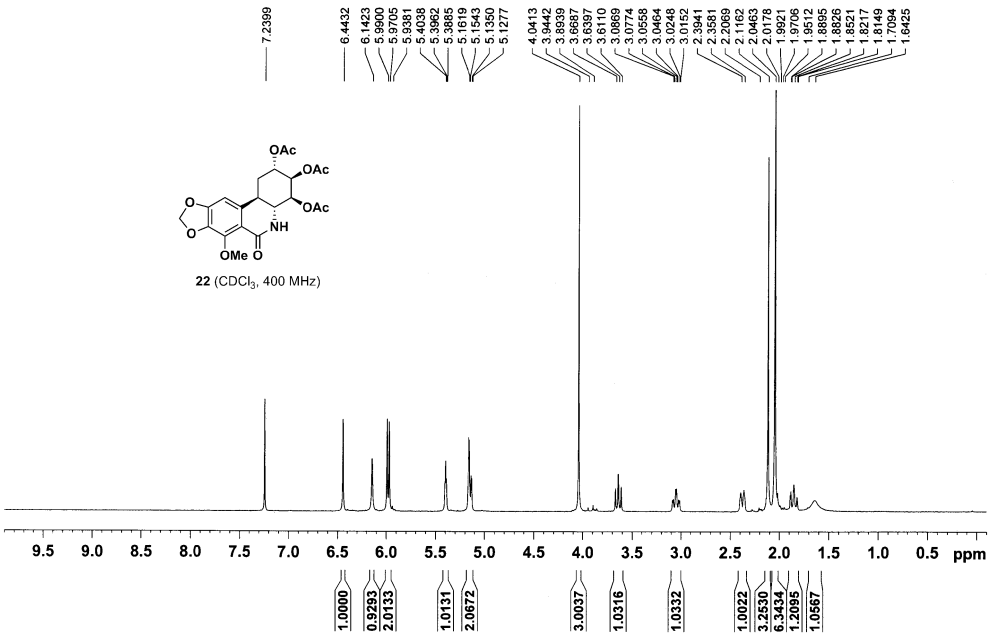
- ^{1}H & ^{13}C NMR spectrum of compound **20**

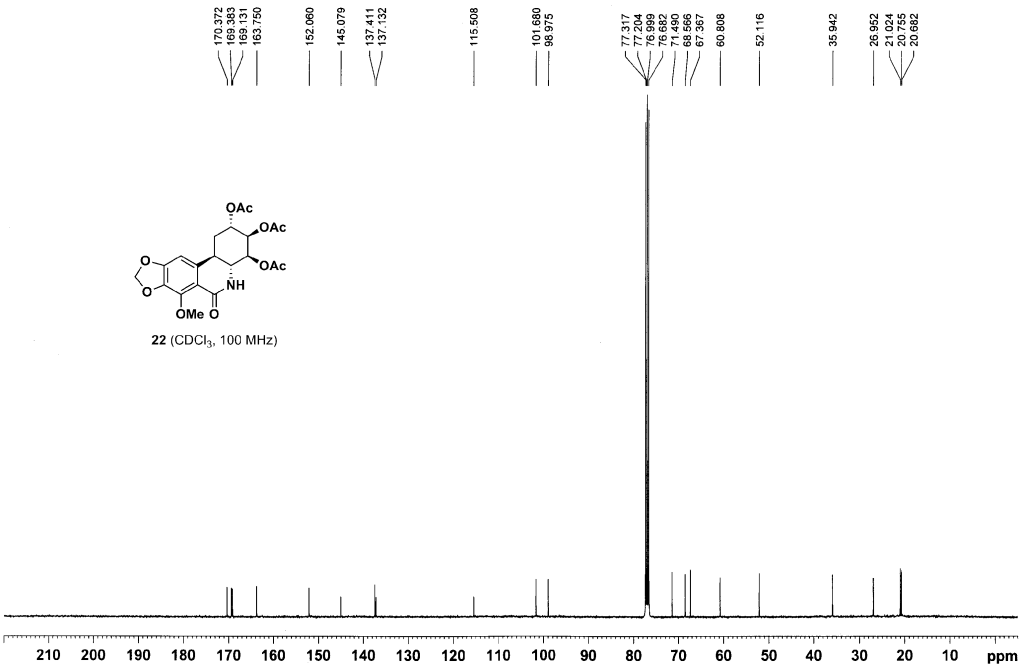


- ^{1}H & ^{13}C NMR spectrum of compound **21**

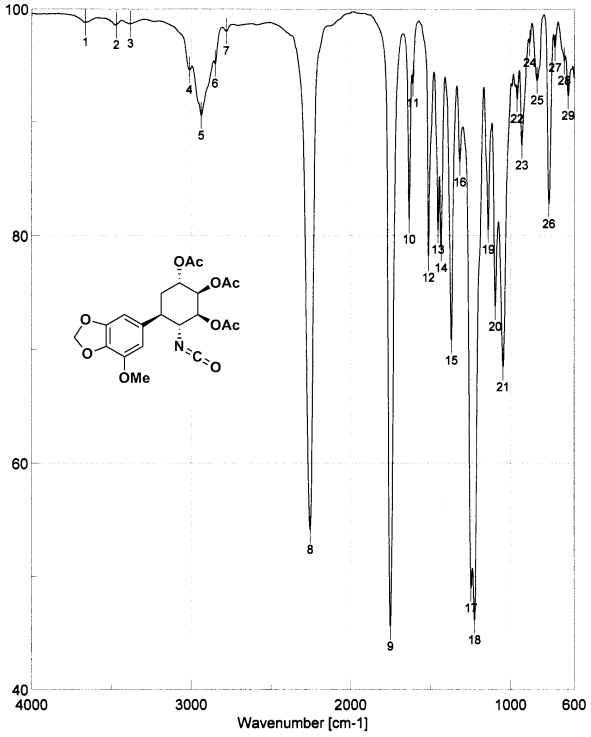


- ^{1}H & ^{13}C NMR spectrum of compound **22**





- IR spectrum of compound **35**



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Comment
User
Division
Company SNU

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Vertical %T
Start 599.753 cm-1
End 4000.6 cm-1
Data pitch 0.964233 cm-1
Data points 3528

[Measurement Information]
Model Name FT/IR-4200typeA
Serial Number B038361018

Light Source Standard
Detector TGS
Accumulation Auto (18)
Resolution 4 cm-1
Zero Filling On
Apodization Cosine
Gain Auto (2)
Aperture Auto (7.1 mm)
Scanning Speed Auto (2 mm/sec)
Filter Auto (30000 Hz)

Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity
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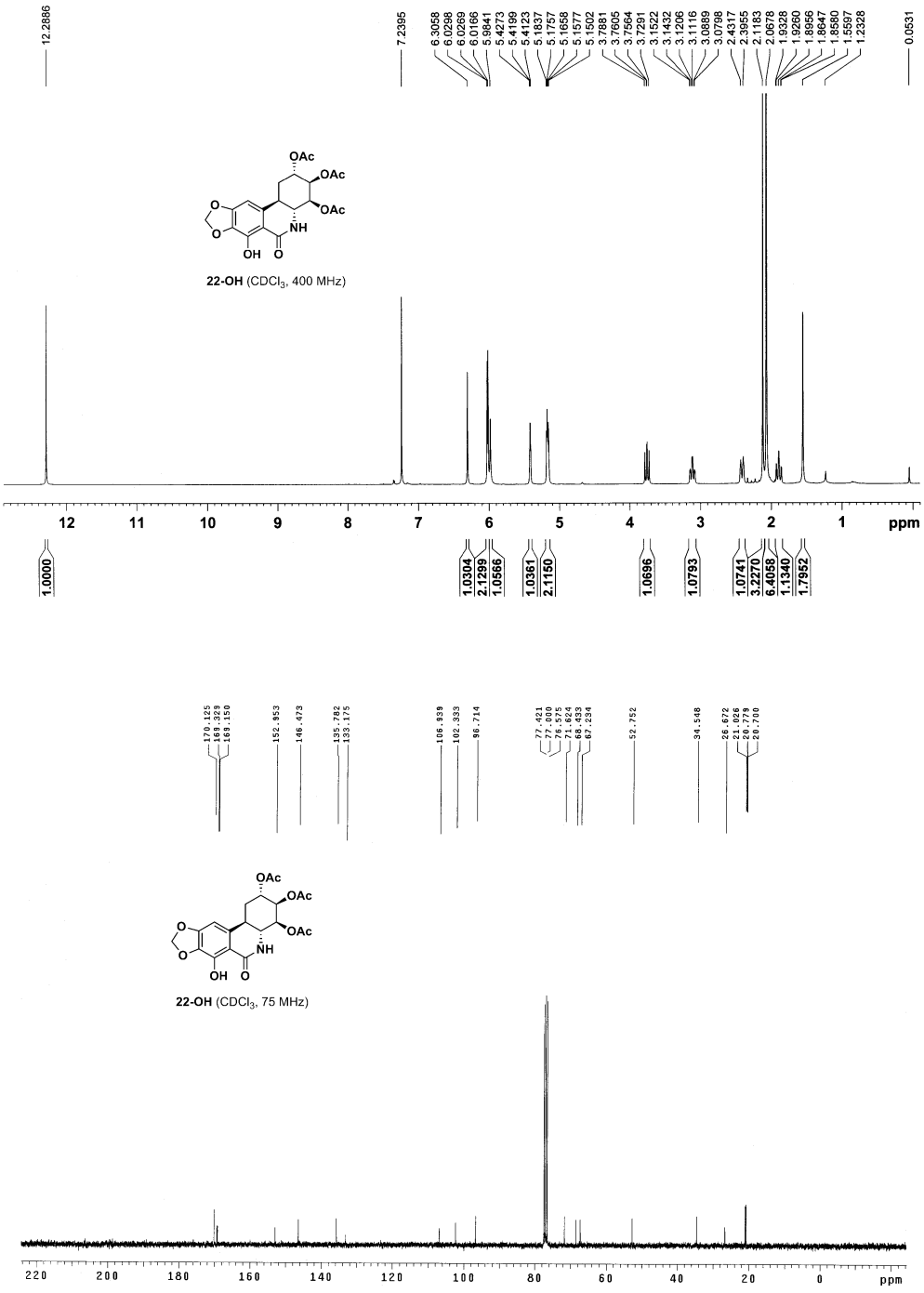
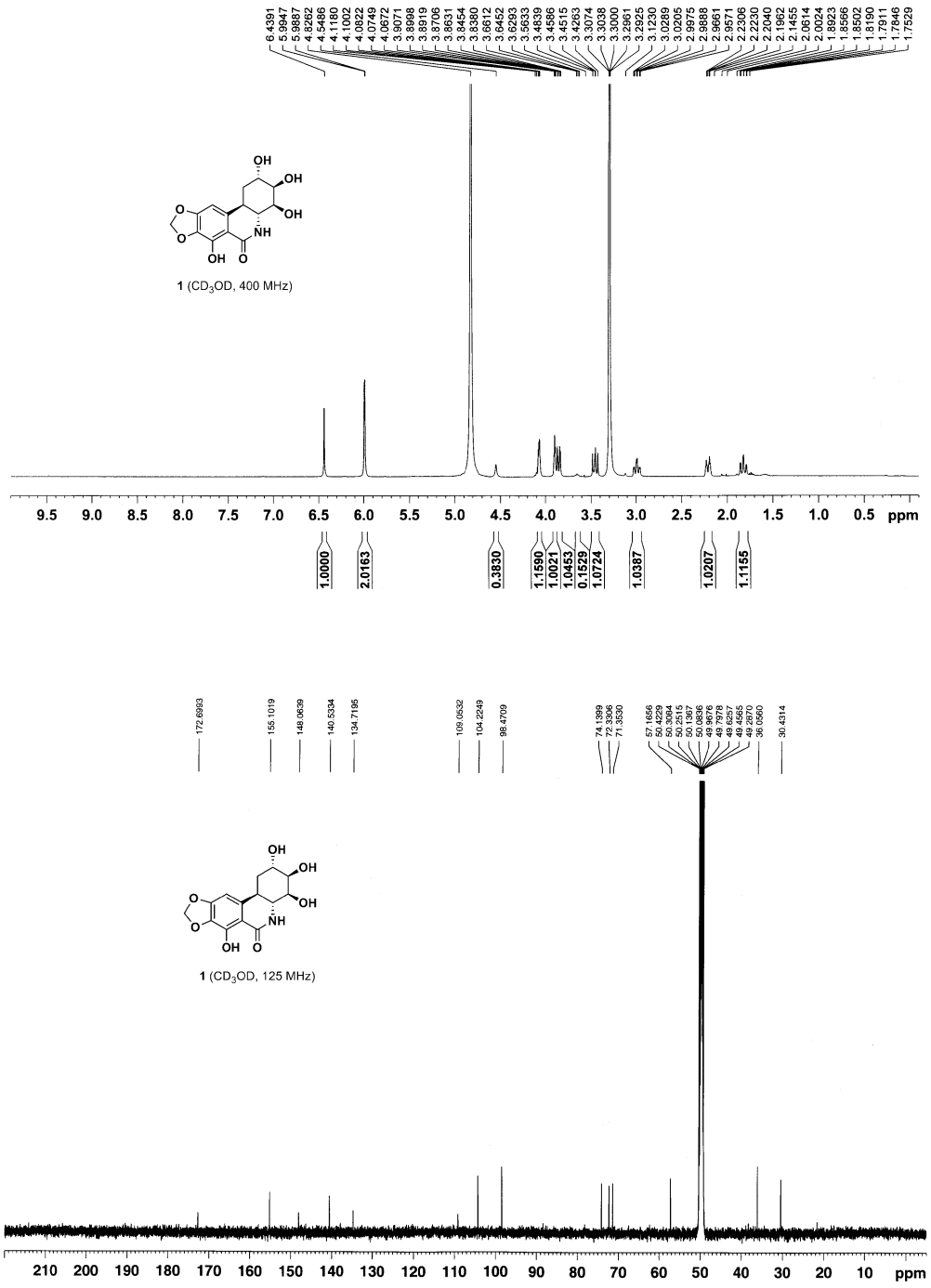
3	3382.53	98.666	4	3014.19	94.5563
5	2938.98	90.5326	6	2852.2	95.1199
7	2781.81	97.9918	8	2253.41	54.1165
9	1752.01	45.5667	10	1634.38	81.4038
11	1613.16	93.3776	12	1513.85	78.0448
13	1453.1	80.5185	14	1434.78	78.8909
15	1370.18	70.7728	16	1318.11	86.4369
17	1245.79	48.961	18	1224.58	46.1513
19	1138.76	80.5075	20	1094.4	73.7498
21	1046.19	68.444	22	959.412	91.9892
23	929.521	87.9136	24	881.309	96.9532
25	834.062	93.6268	26	757.888	82.7728
27	722.211	96.5186	28	664.357	95.3673
29	639.287	92.2801			

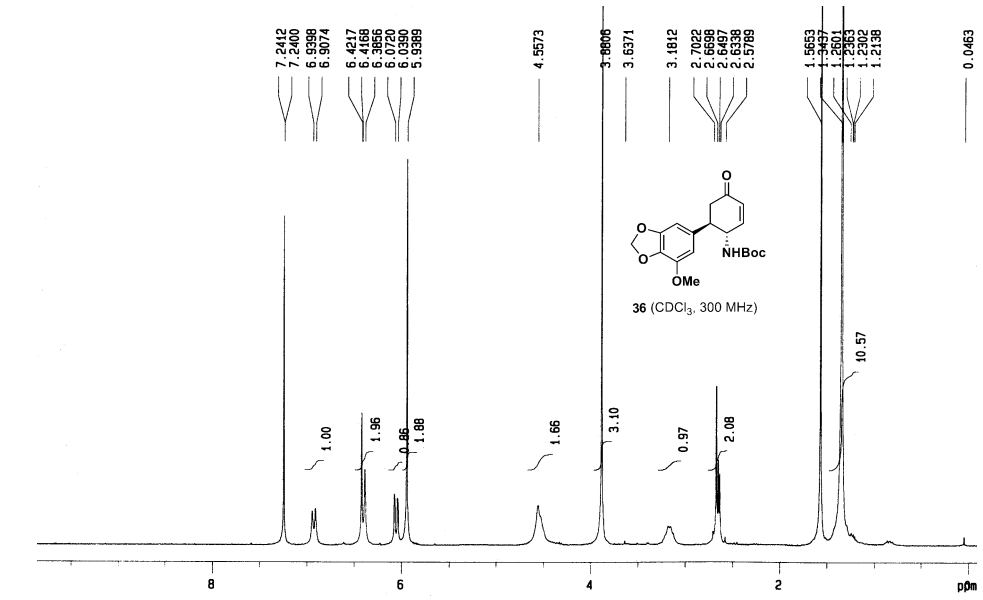
- ^{1}H & ^{13}C NMR spectrum of compound **22-OH**

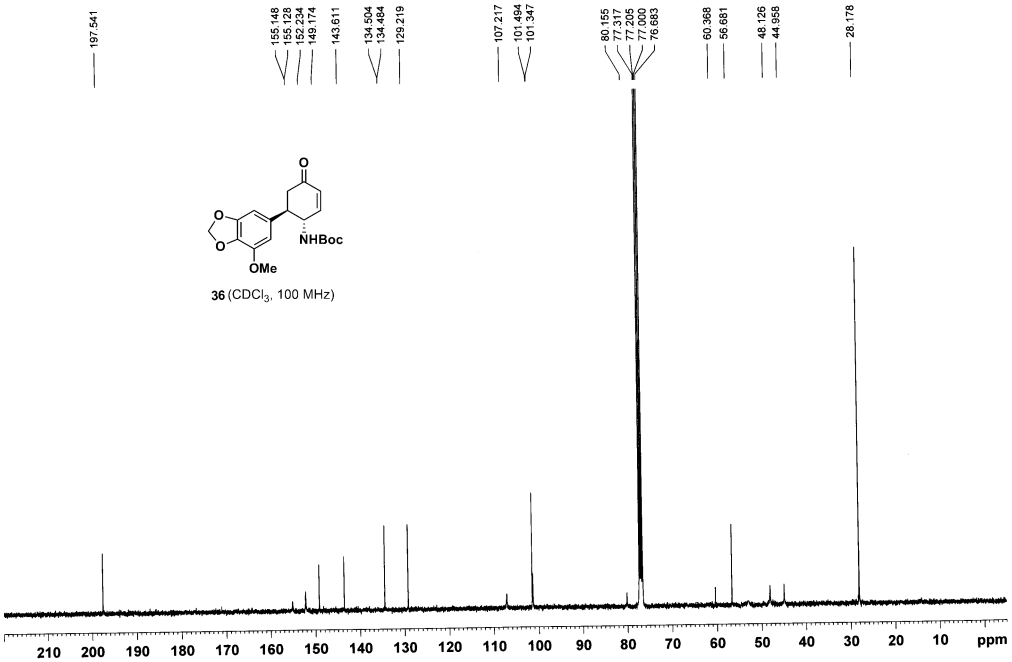


- ^{1}H & ^{13}C NMR spectrum of compound **1**

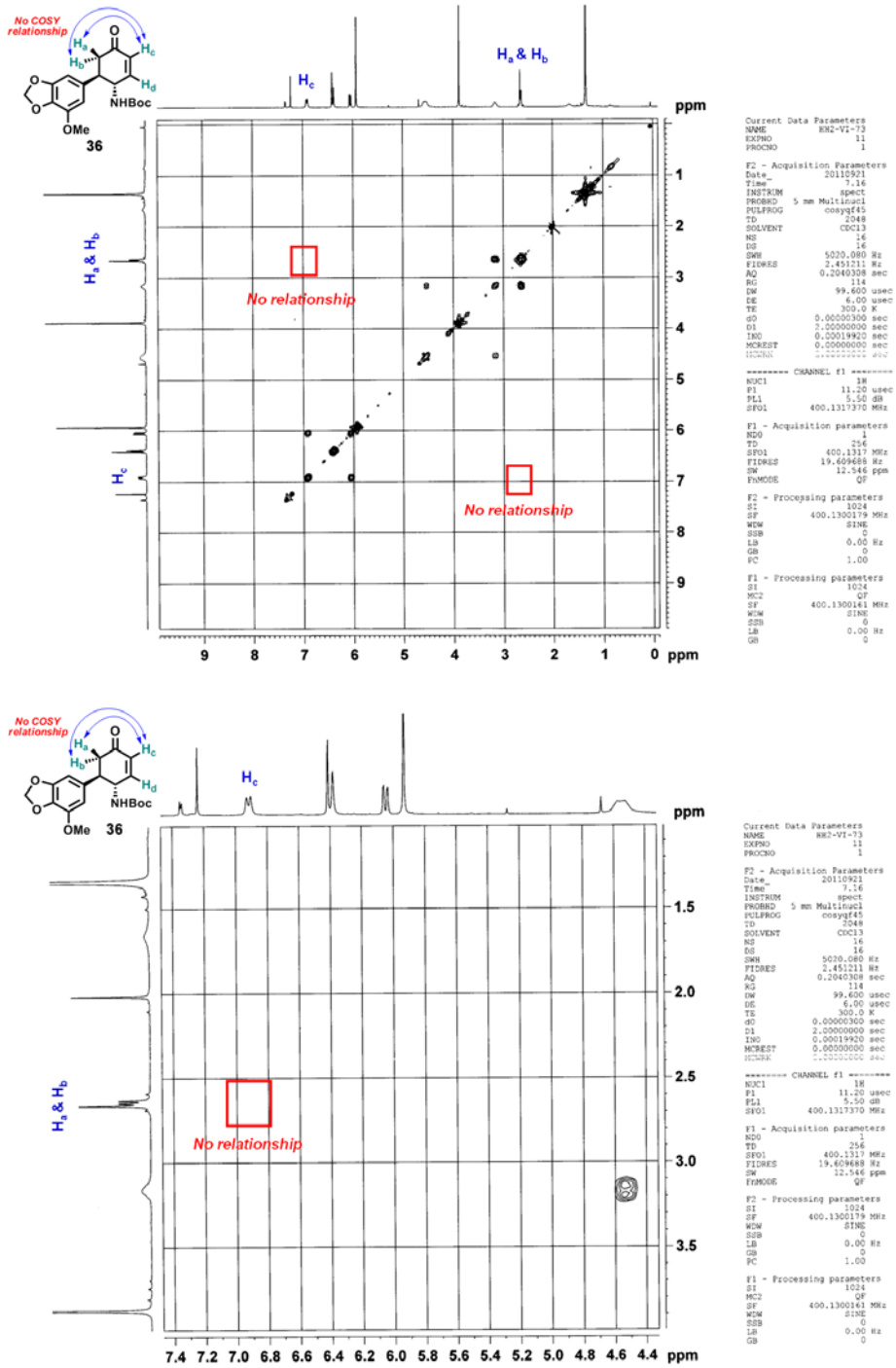


- ^{1}H & ^{13}C NMR spectrum of compound **36**

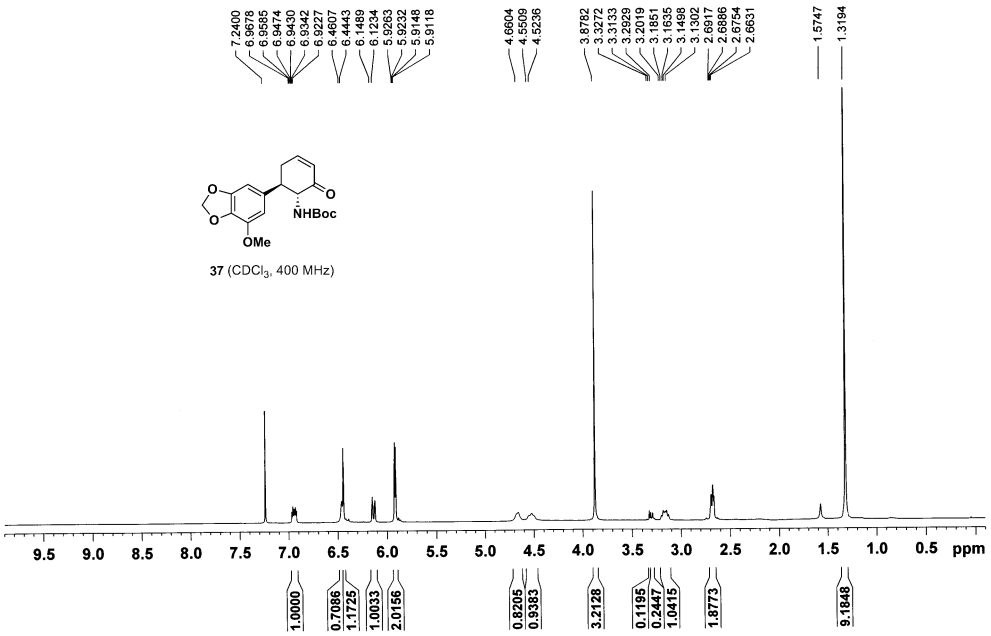


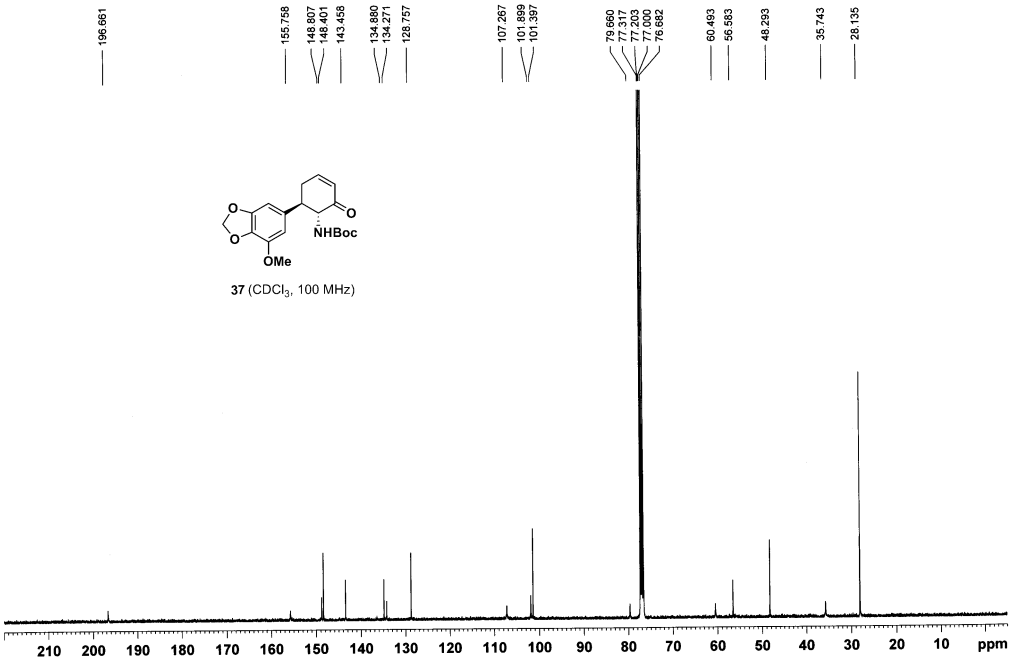


- ^{1}H-^{1}H COSY NMR spectrum of compound **36**

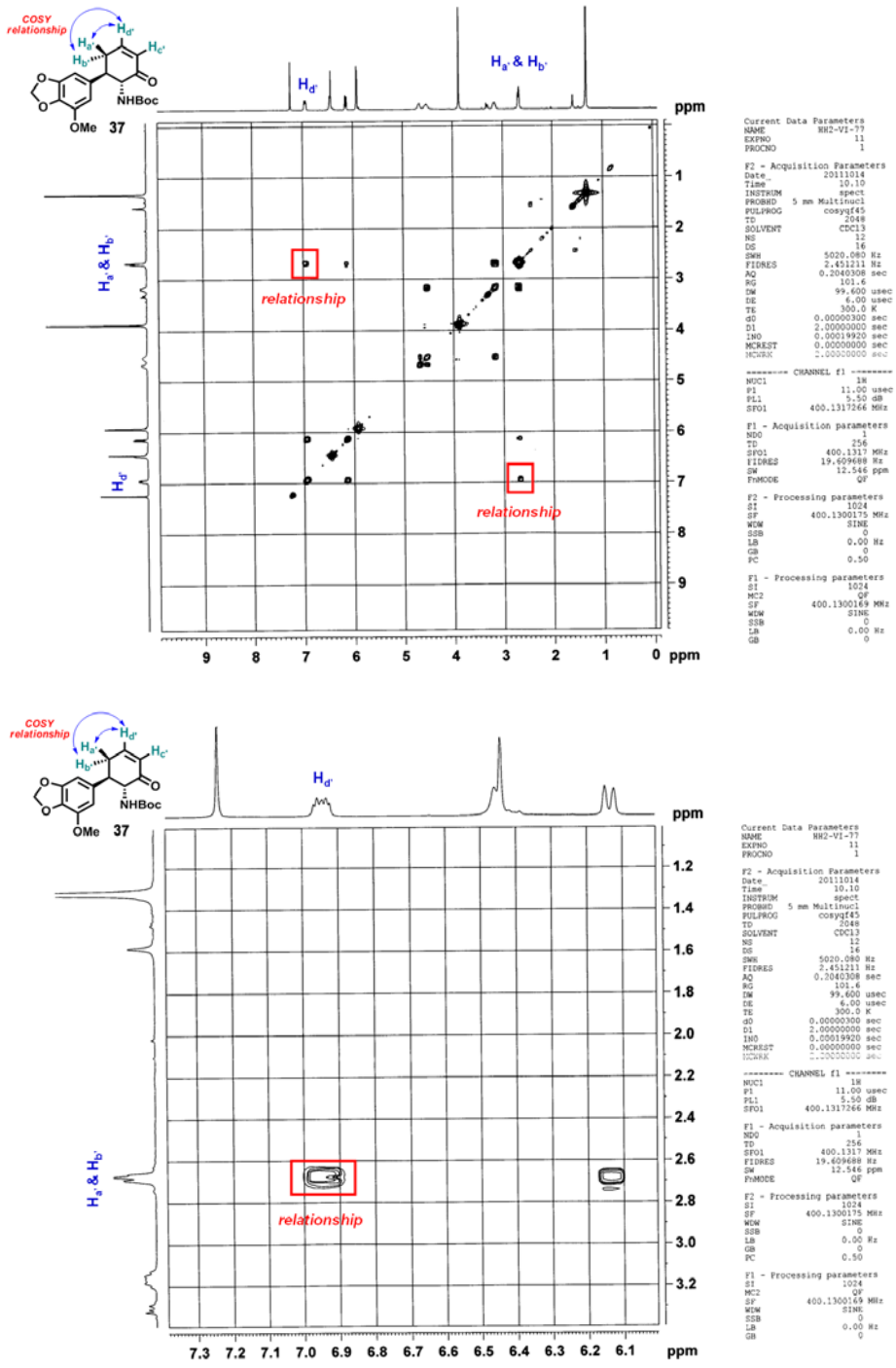


- ^{1}H & ^{13}C NMR spectrum of compound **37**

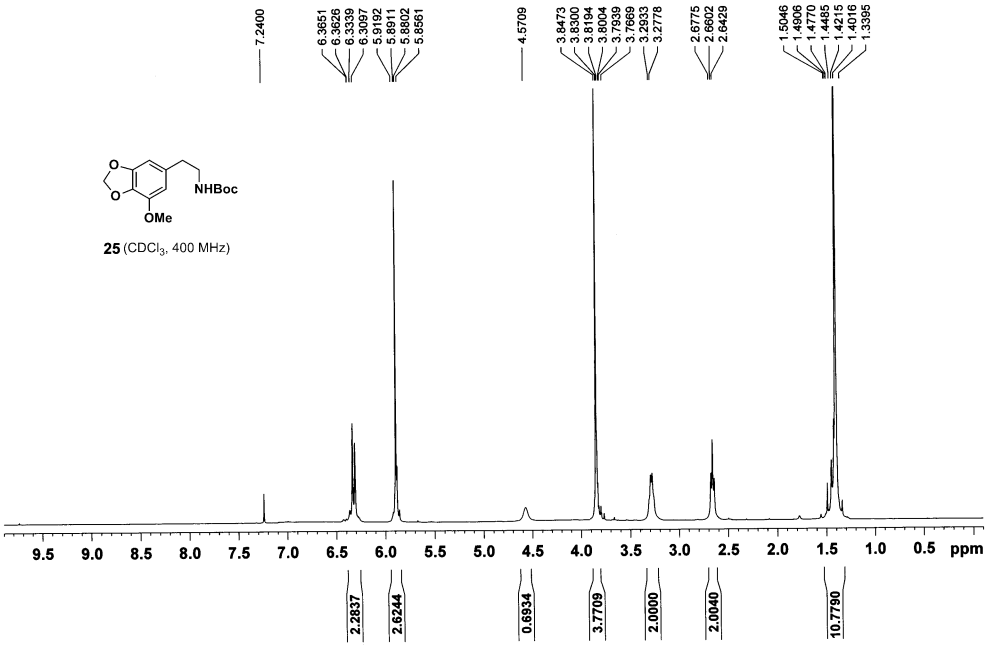


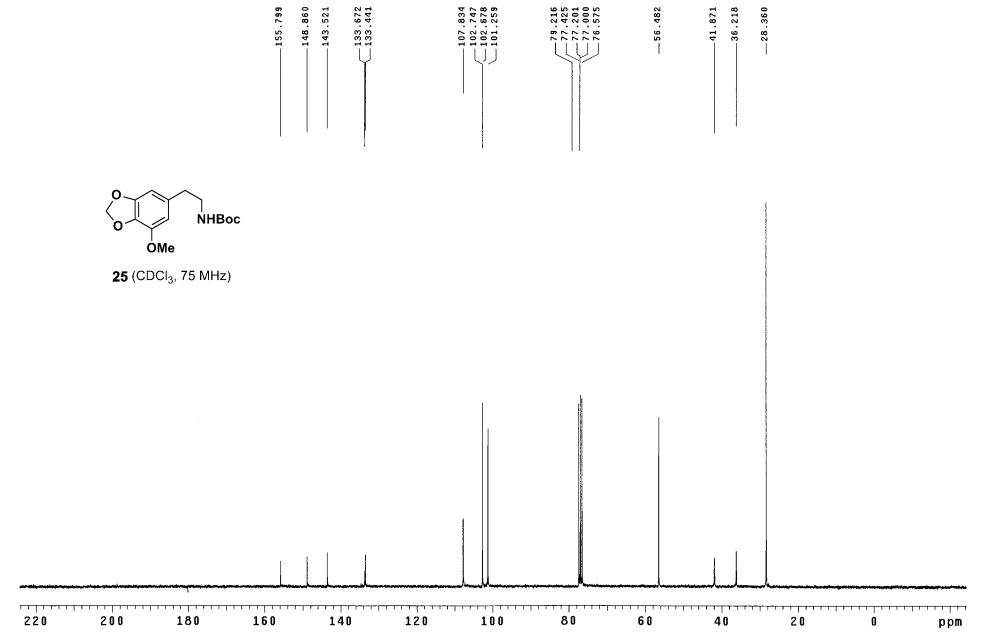


- ^{1}H-^{1}H COSY NMR spectrum of compound **37**

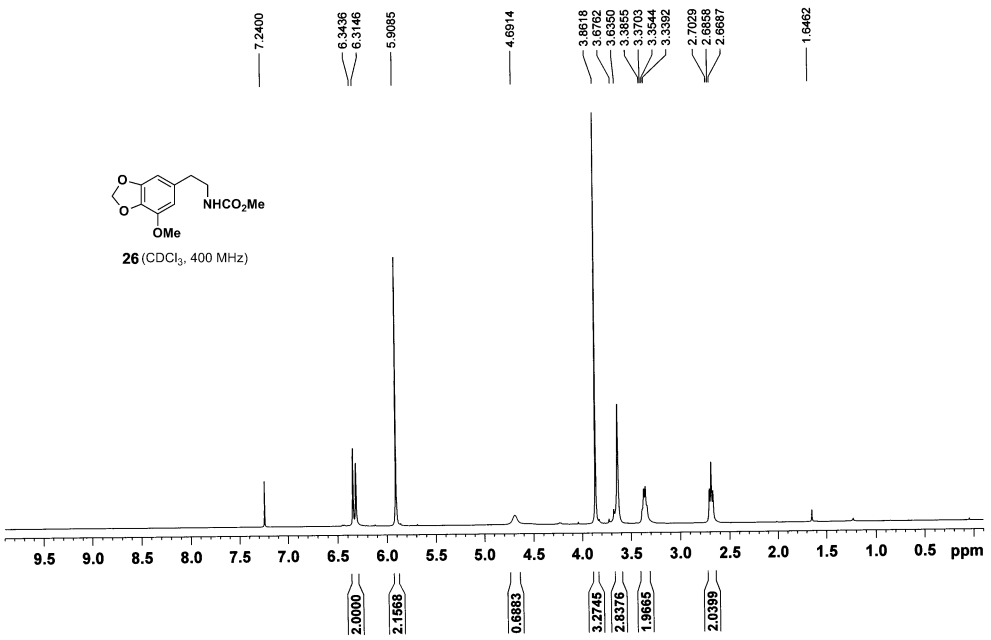


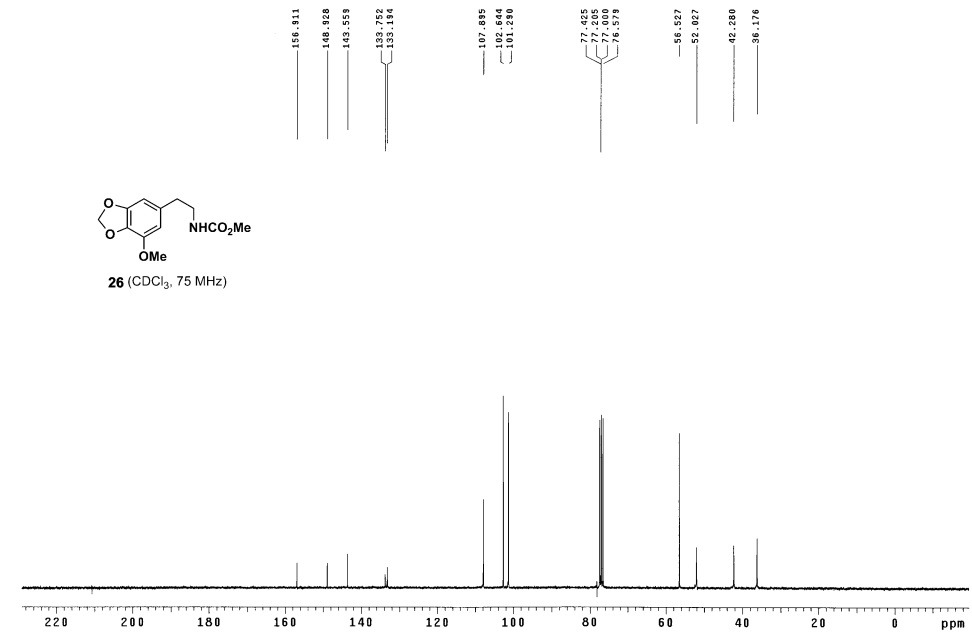
- ^{1}H & ^{13}C NMR spectrum of compound **25**



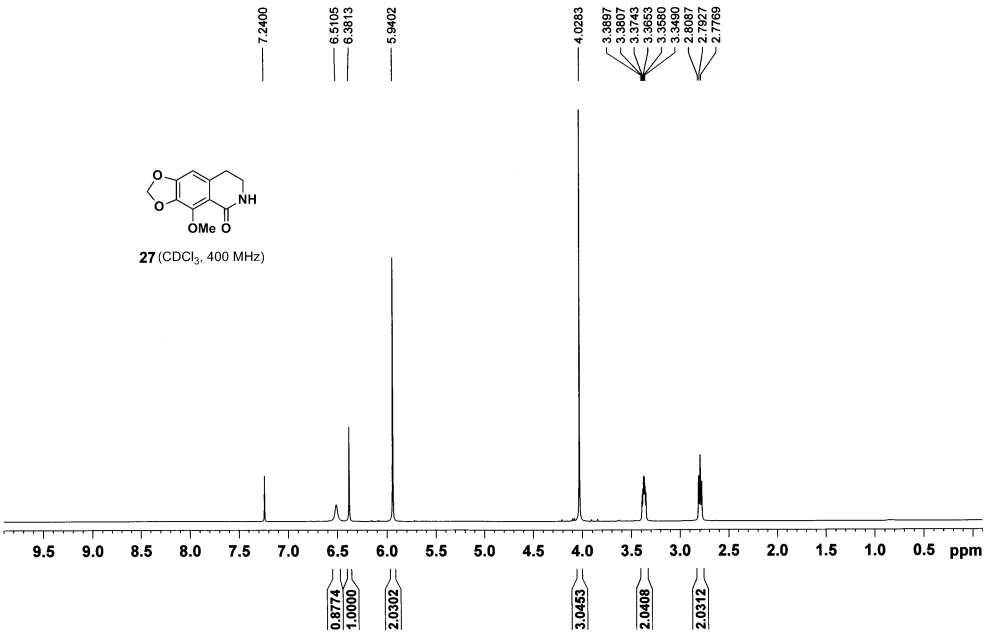


- ^{1}H & ^{13}C NMR spectrum of compound **26**

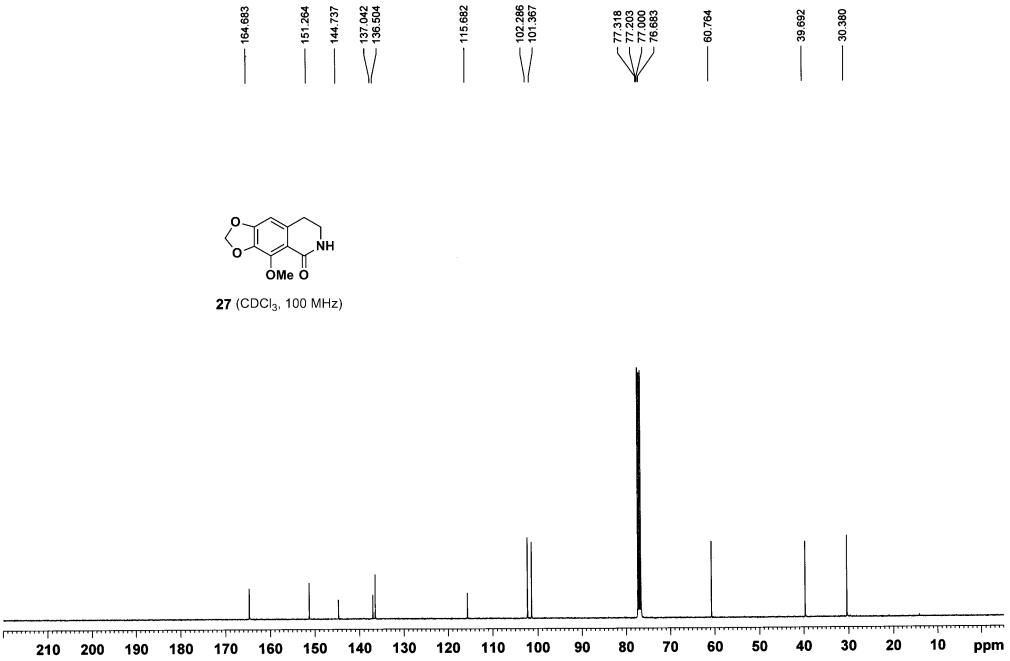




- ^{1}H & ^{13}C NMR spectrum of compound **27**

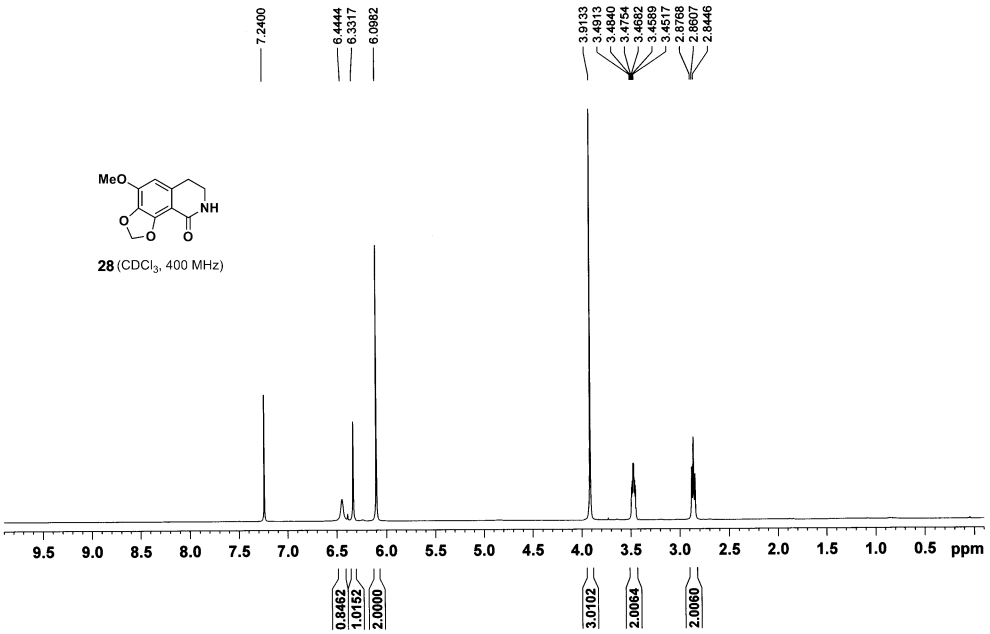


27 ($CDCl_3$, 400 MHz)

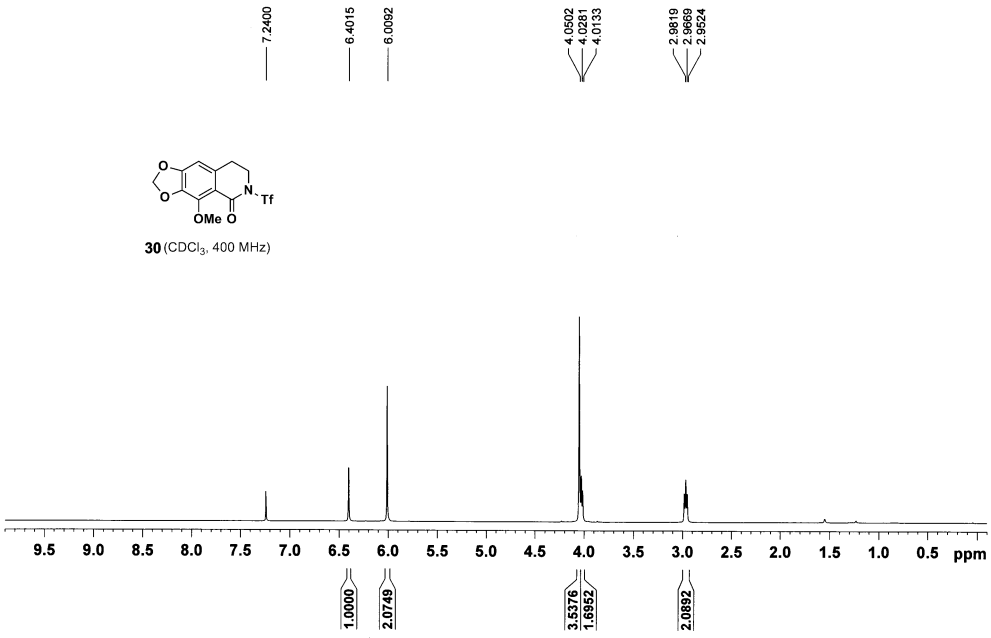


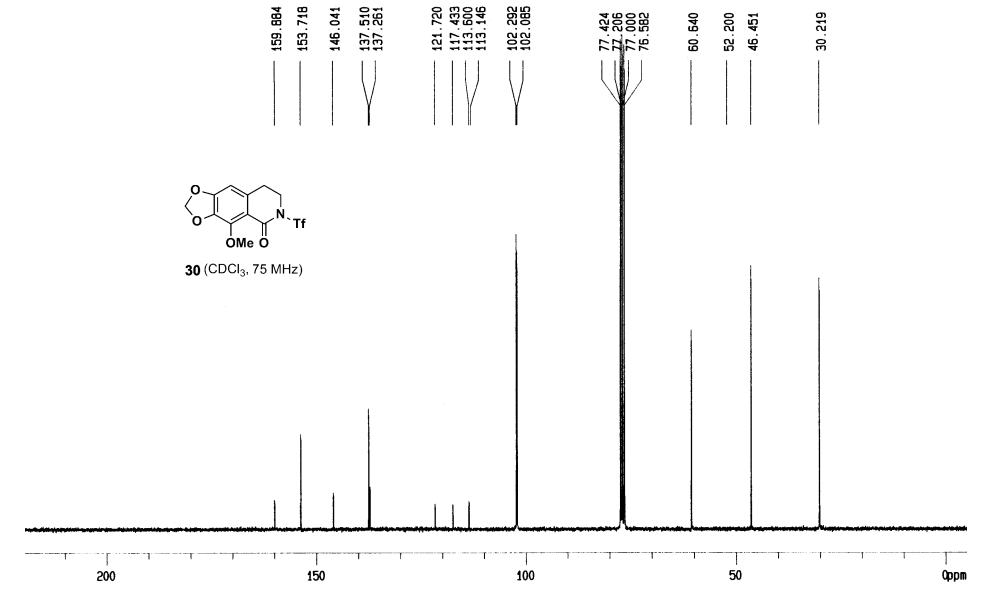
27 ($CDCl_3$, 100 MHz)

- ^{1}H NMR spectrum of compound **28**

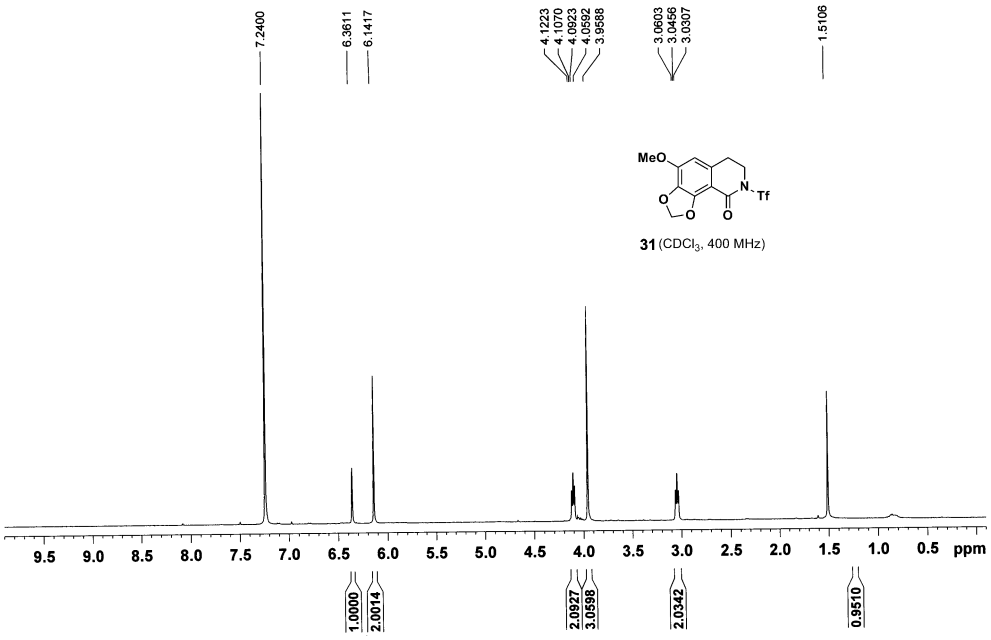


- ^{1}H & ^{13}C NMR spectrum of compound **30**

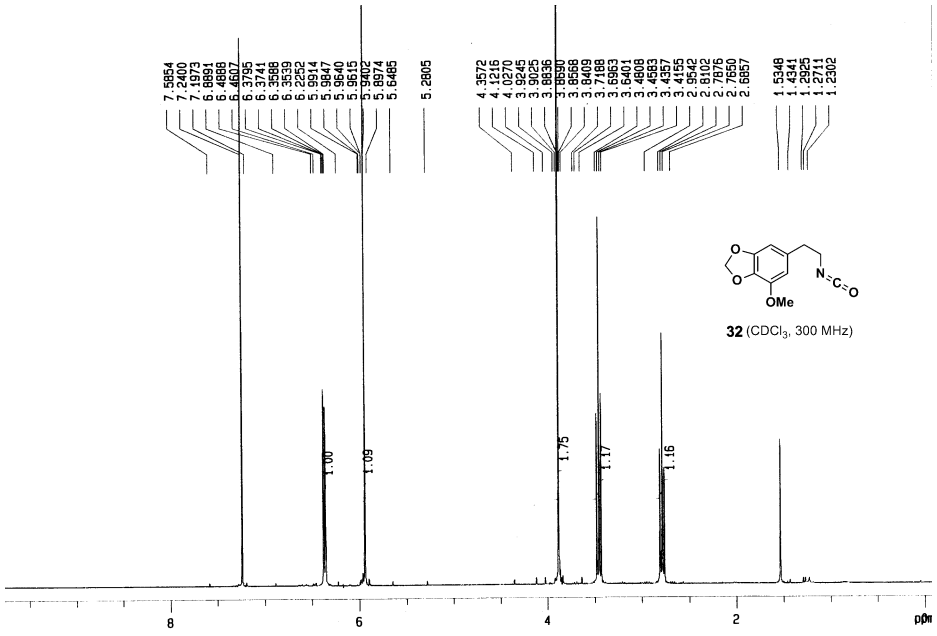


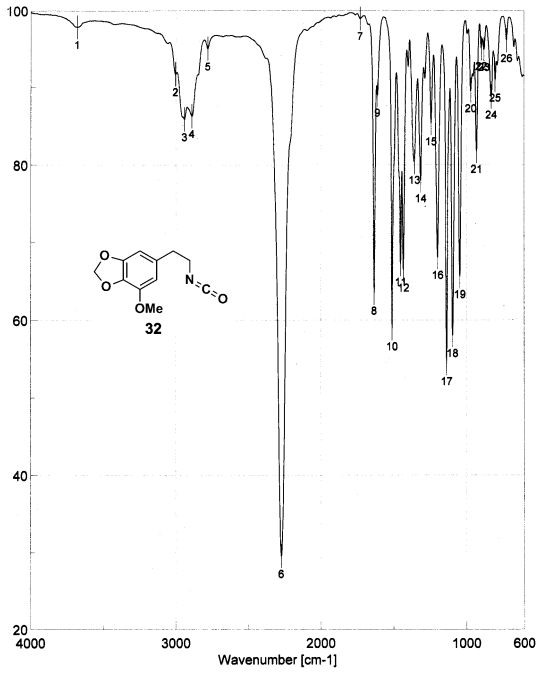


- ^{1}H NMR spectrum of compound **31**



- ^{1}H NMR & IR spectrum of compound **32**





[Comment]
Sample Name CH-IV-39 (isocyanate)
Comment
User
Division
Company SNU

[Data Information]
Creation Date 2012-02-07 오 5:27

Data array type Linear data array
Horizontal Wavenumber [cm-1]
Vertical %T
Start 599.753 cm-1
End 4000.6 cm-1
Data pitch 0.964233 cm-1
Data points 3528

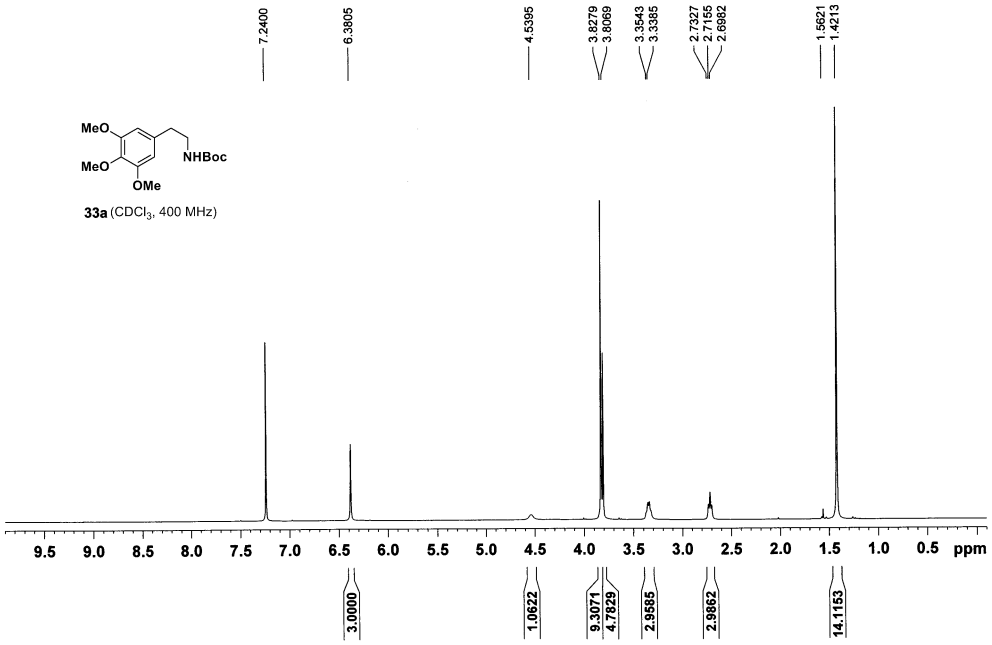
[Measurement Information]
Model Name FT/IR-4200typeA
Serial Number B038361018

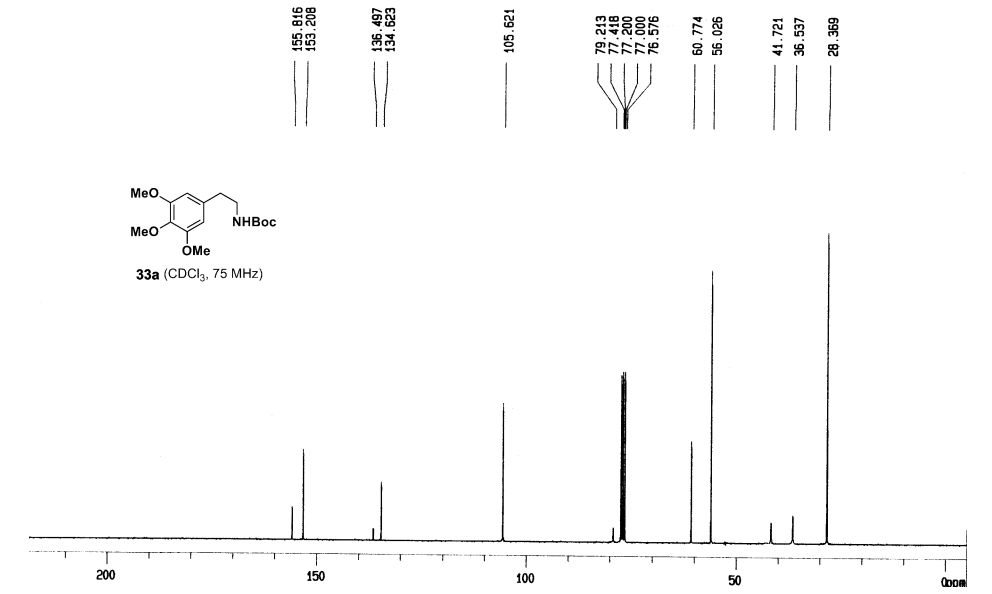
Light Source Standard
Detector TGS
Accumulation Auto (18)
Resolution 4 cm-1
Zero Filling On
Apodization Cosine
Gain Auto (2)
Aperture Auto (7.1 mm)
Scanning Speed Auto (2 mm/sec)
Filter Auto (30000 Hz)

Result of Peak Picking

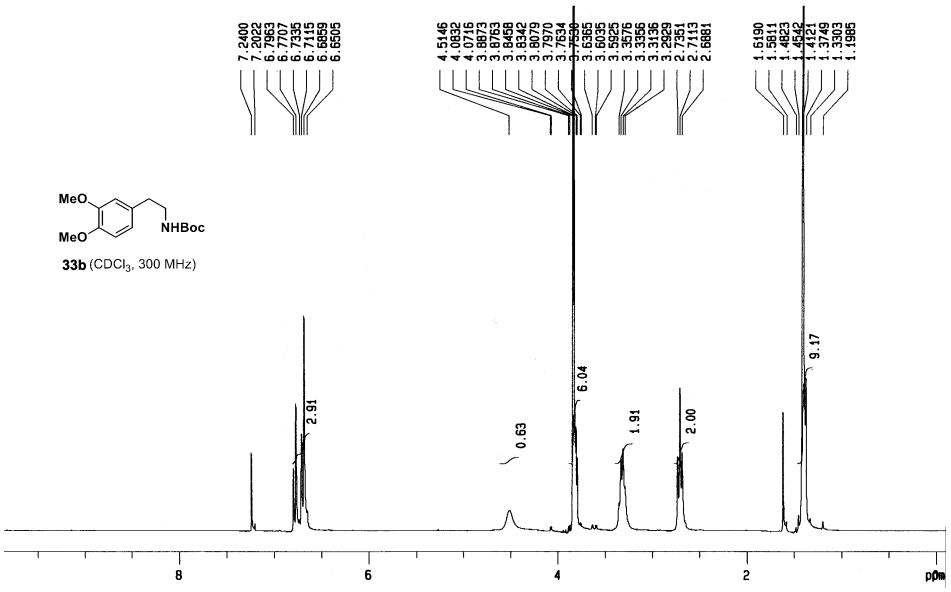
No.	Position	Intensity	No.	Position	Intensity
1	3682.41	97.8366	2	3004.55	91.6776
3	2942.84	85.8517	4	2891.74	86.2829
5	2781.81	95.0251	6	2273.66	29.5089
7	1731.76	98.9819	8	1634.38	63.5163
9	1612.2	89.0503	10	1511.92	58.9036
11	1452.14	67.2503	12	1432.85	66.4867
13	1357.64	80.3441	14	1313.29	77.9904
15	1241.93	85.3262	16	1196.61	68.1357
17	1133.94	54.3929	18	1093.44	58.0385
19	1044.26	65.6256	20	969.055	89.5679
21	929.521	81.7457	22	896.737	95.074
23	878.417	94.9228	24	827.312	88.7428
25	800.314	90.9463	26	722.211	96.0627

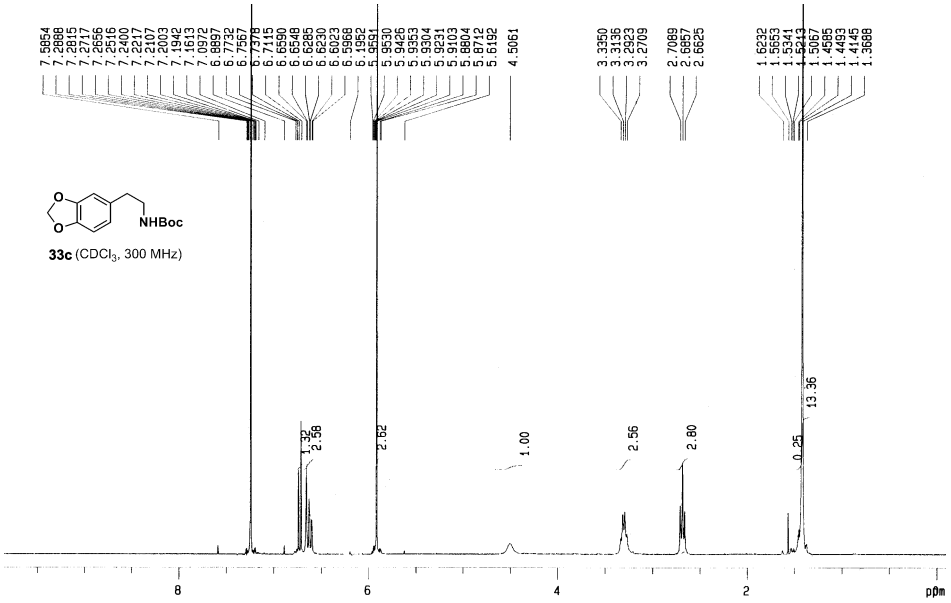
- ^{1}H & ^{13}C NMR spectrum of compound **33a**



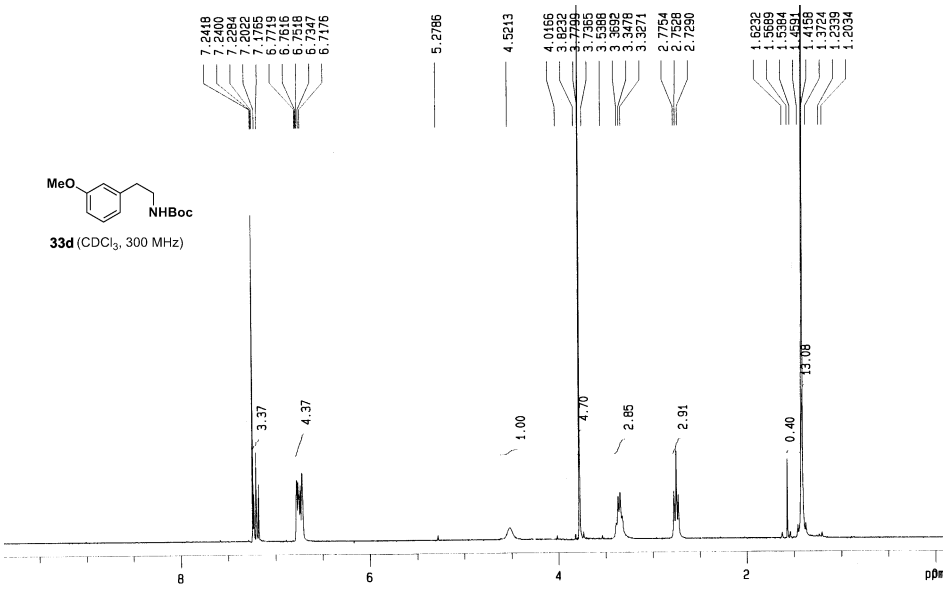


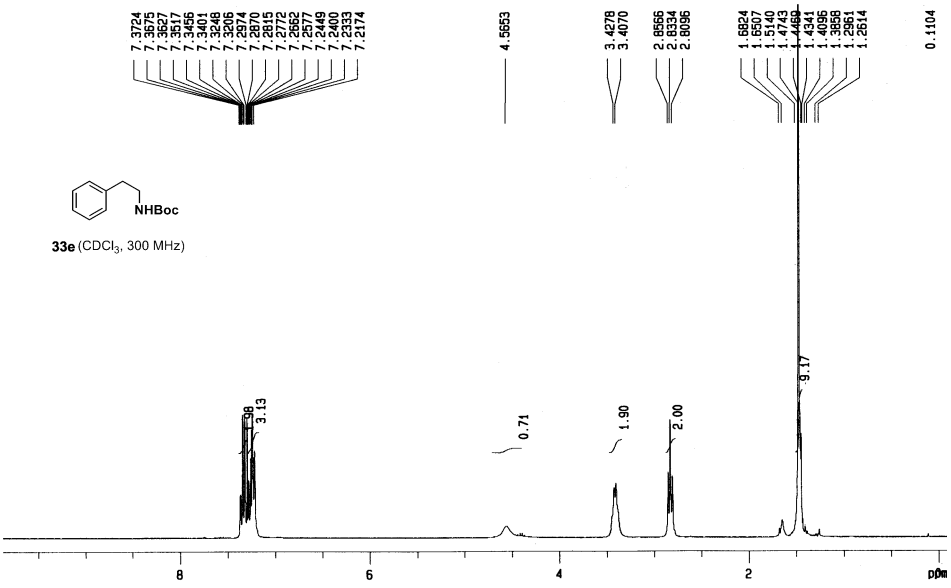
- ^{1}H NMR spectrum of compound **33b** and **33c**



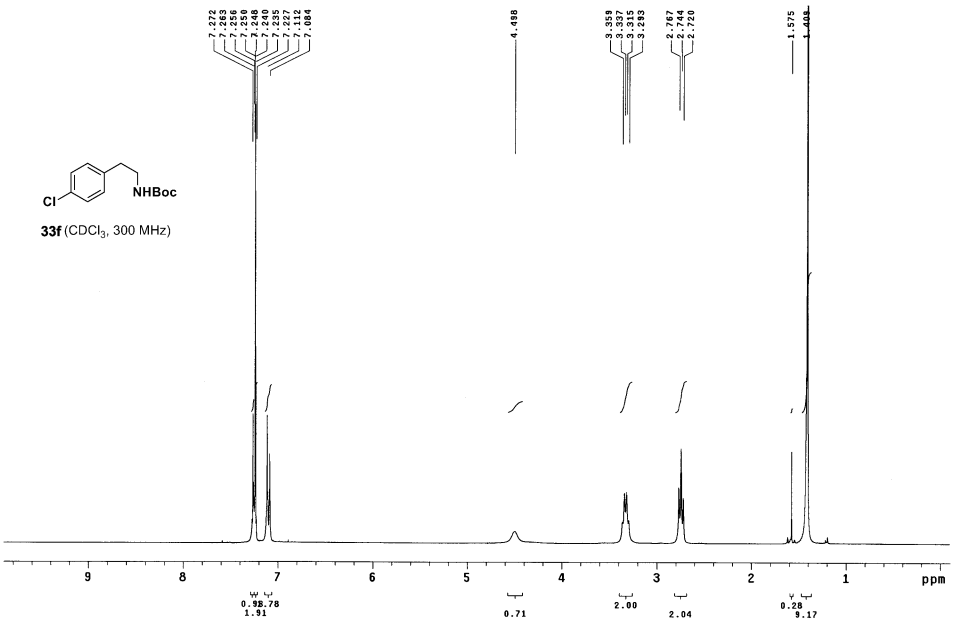


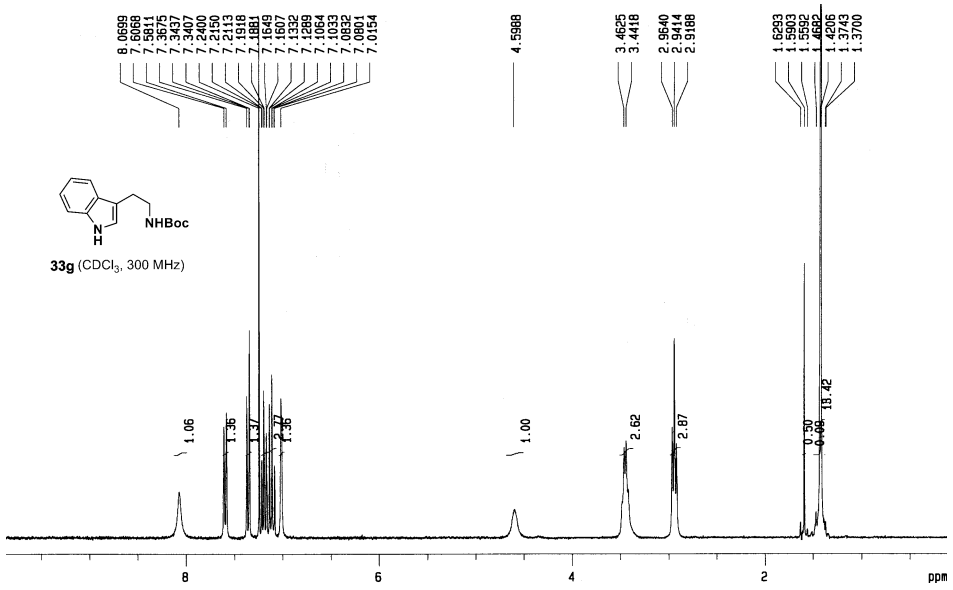
- ^{1}H NMR spectrum of compound **33d** and **33e**



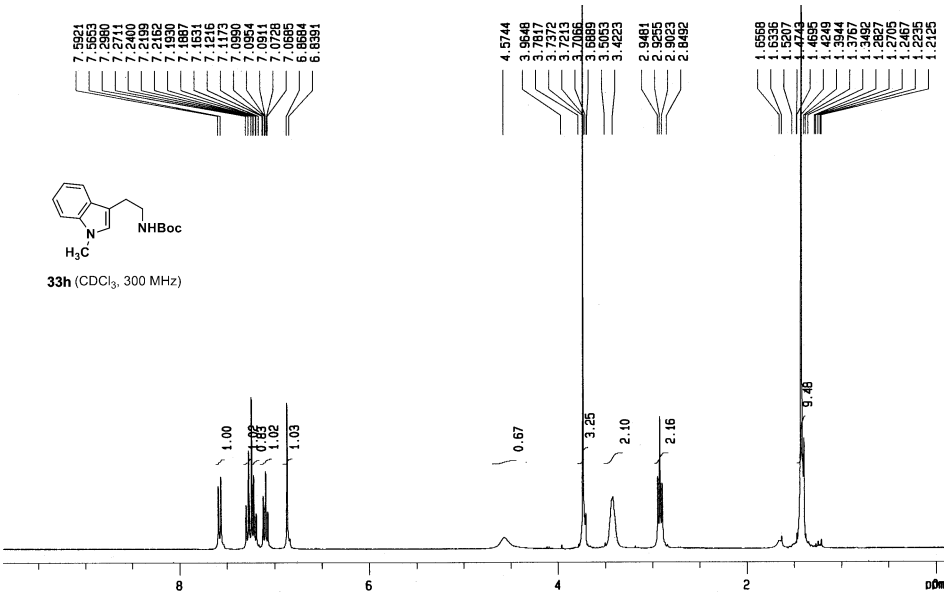


- ^{1}H NMR spectrum of compound **33f** and **33g**

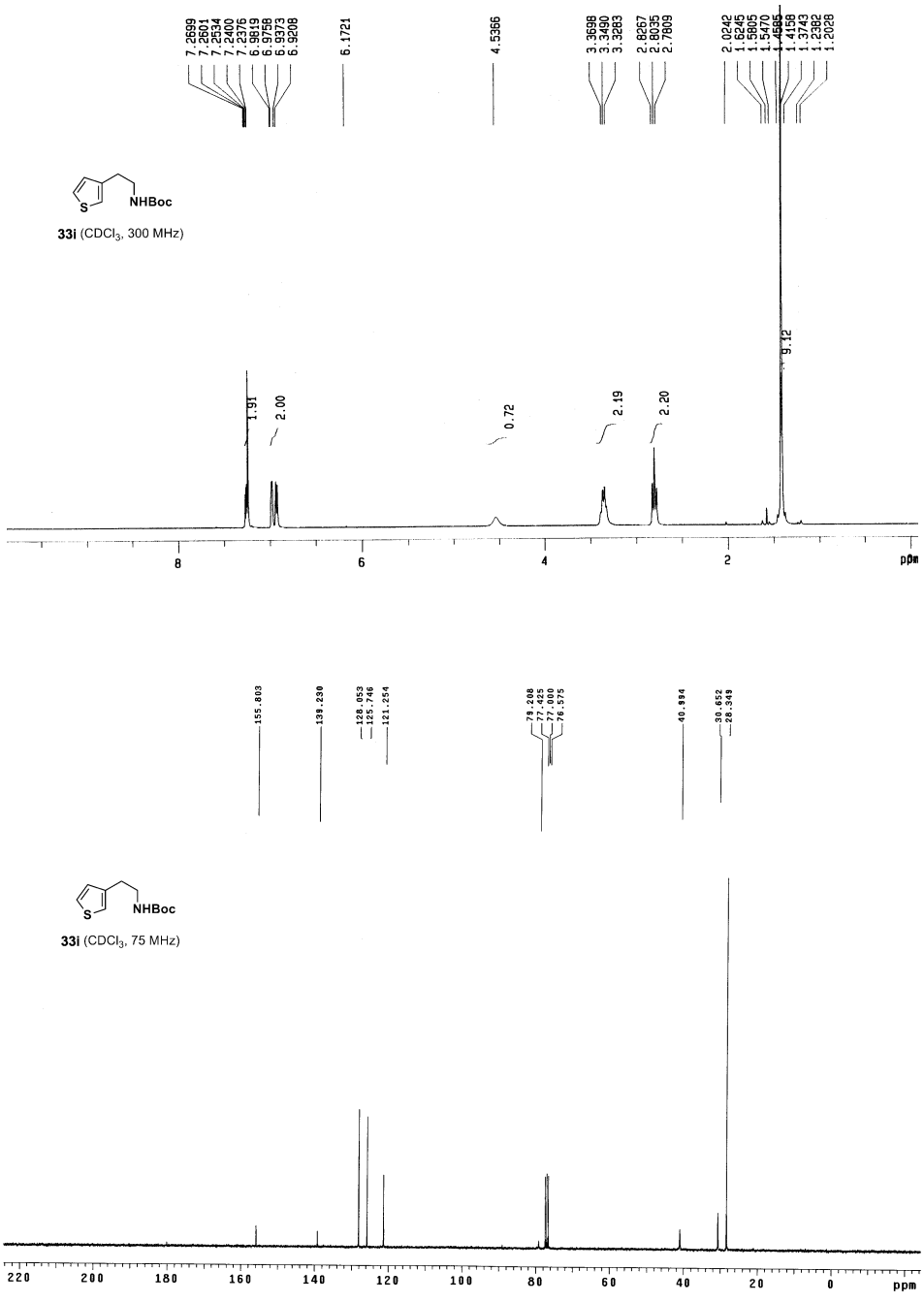




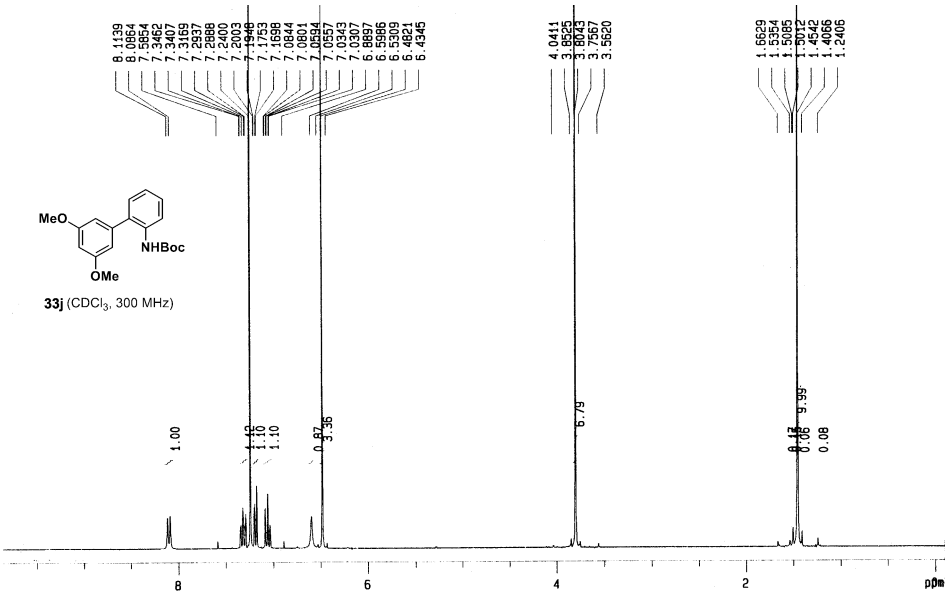
- ^{1}H NMR spectrum of compound **33h**



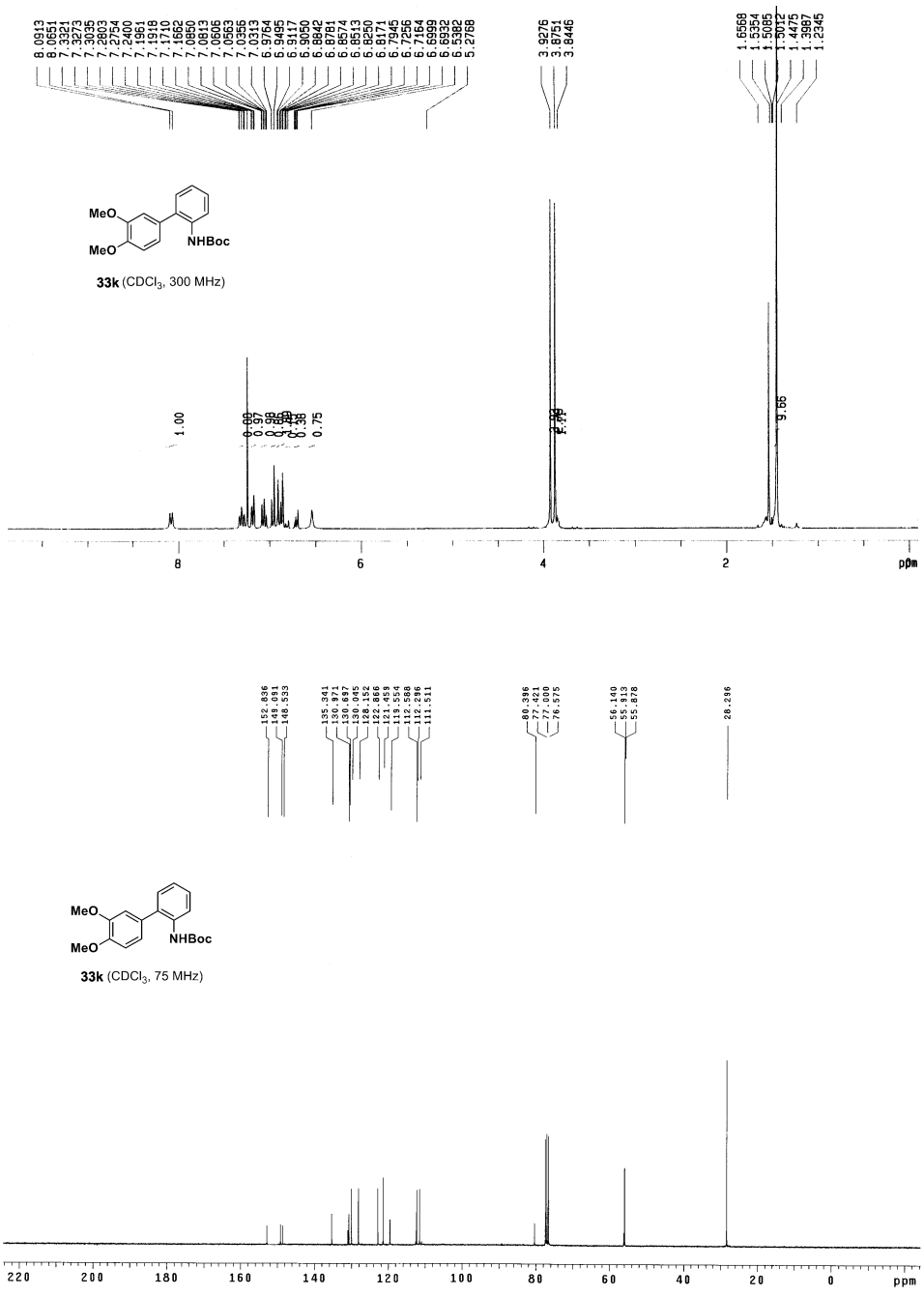
- ^{1}H & ^{13}C NMR spectrum of compound **33i**



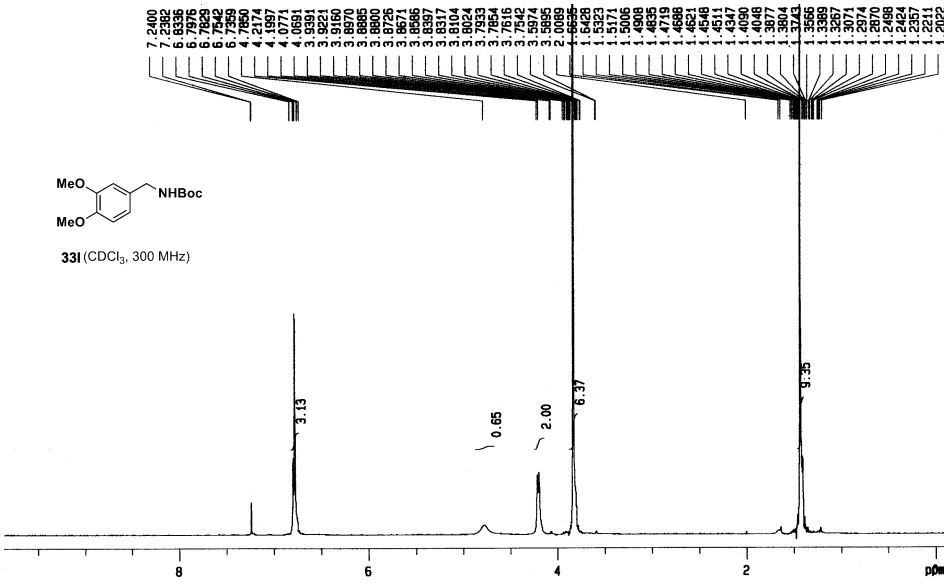
- ^{1}H NMR spectrum of compound **33j**



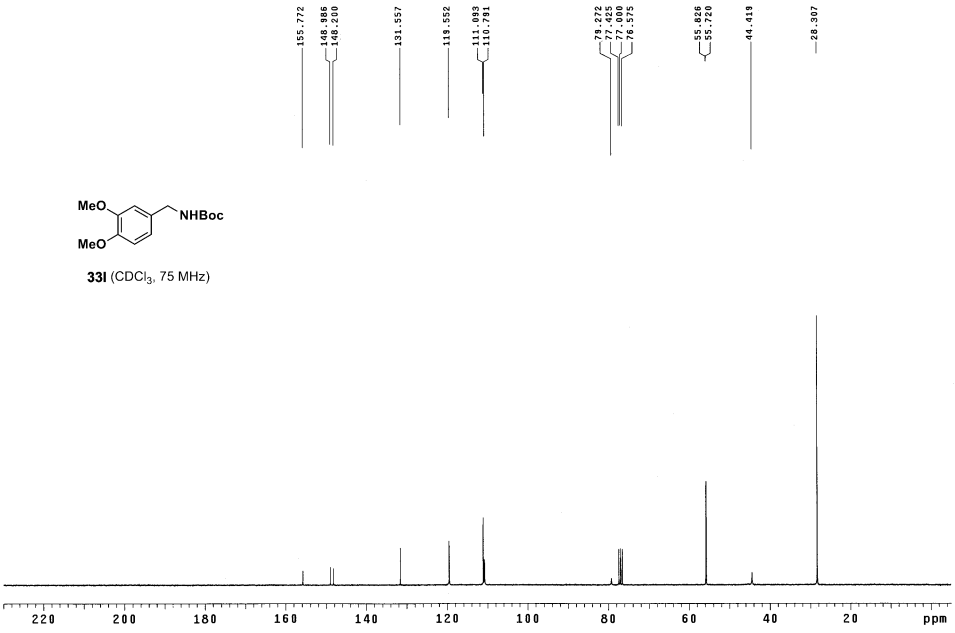
- ^{1}H & ^{13}C NMR spectrum of compound **33k**



- ^{1}H & ^{13}C NMR spectrum of compound **33l**

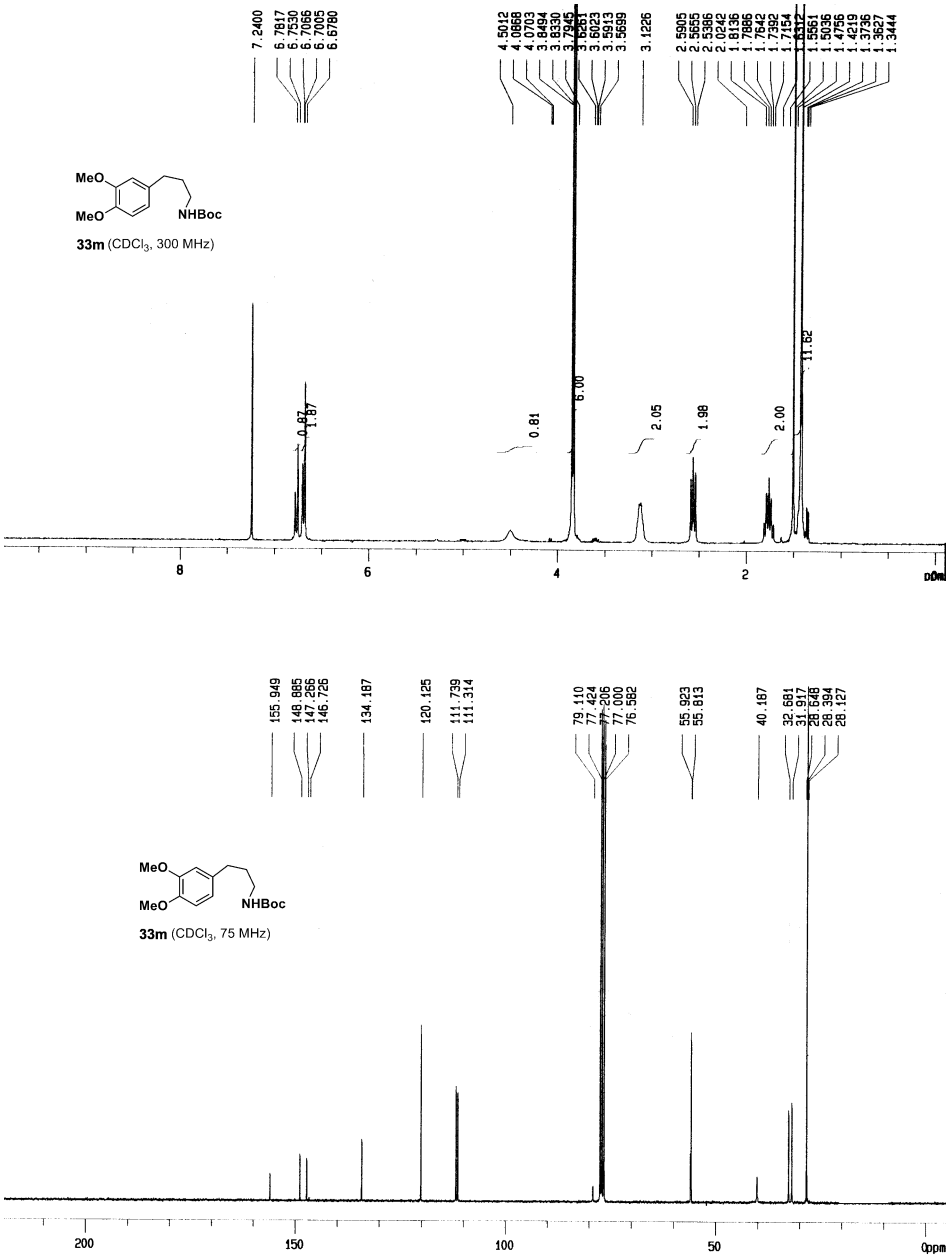


33l ($CDCl_3$, 300 MHz)

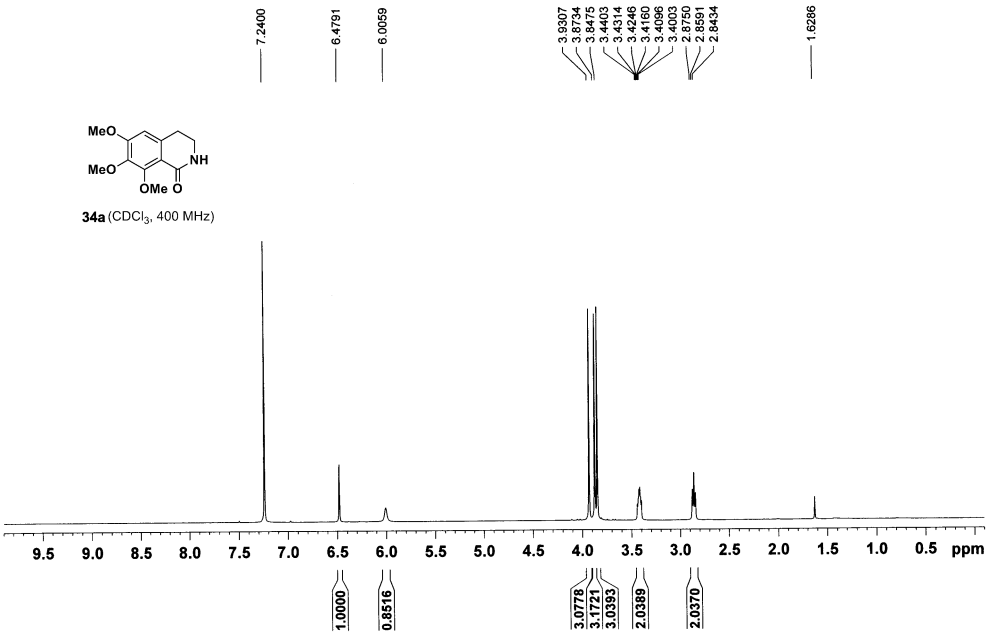


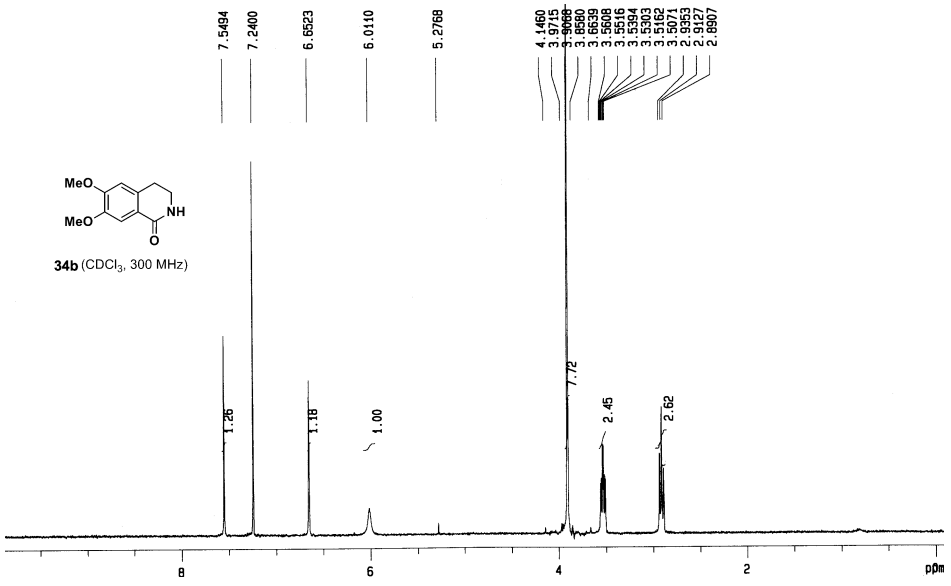
33l ($CDCl_3$, 75 MHz)

- ^{1}H & ^{13}C NMR spectrum of compound **33m**

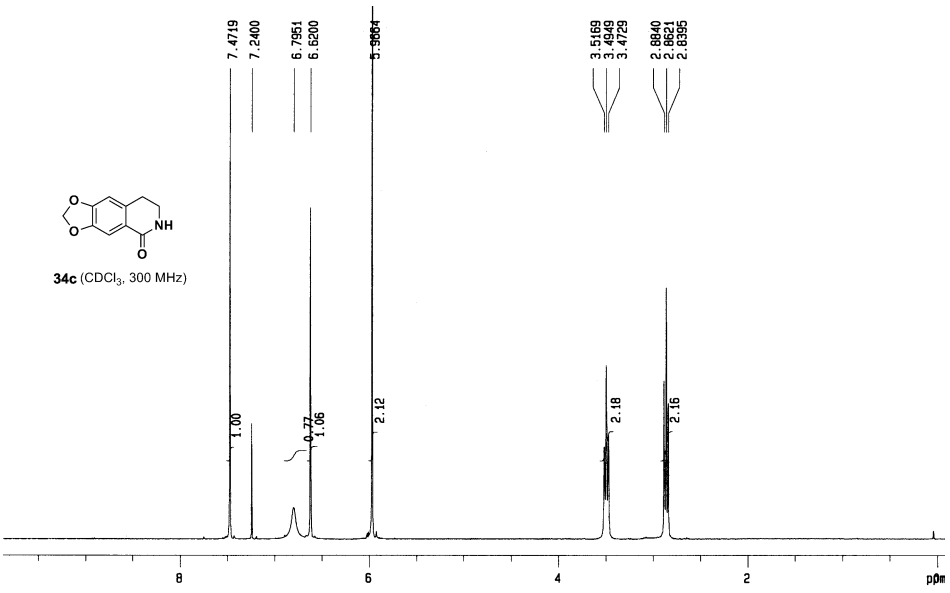


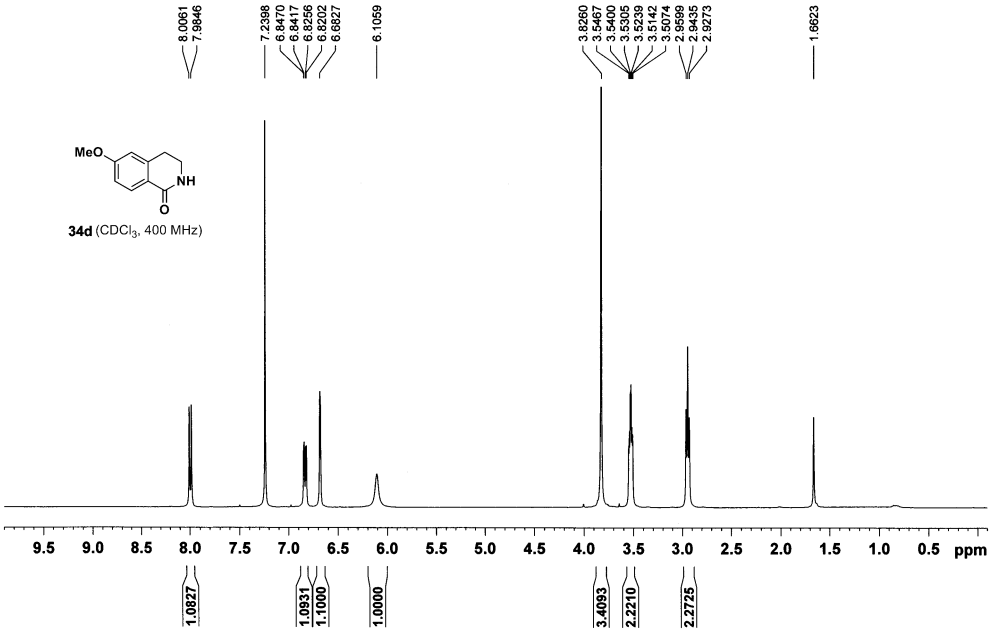
- ^{1}H NMR spectrum of compound **34a** and **34b**



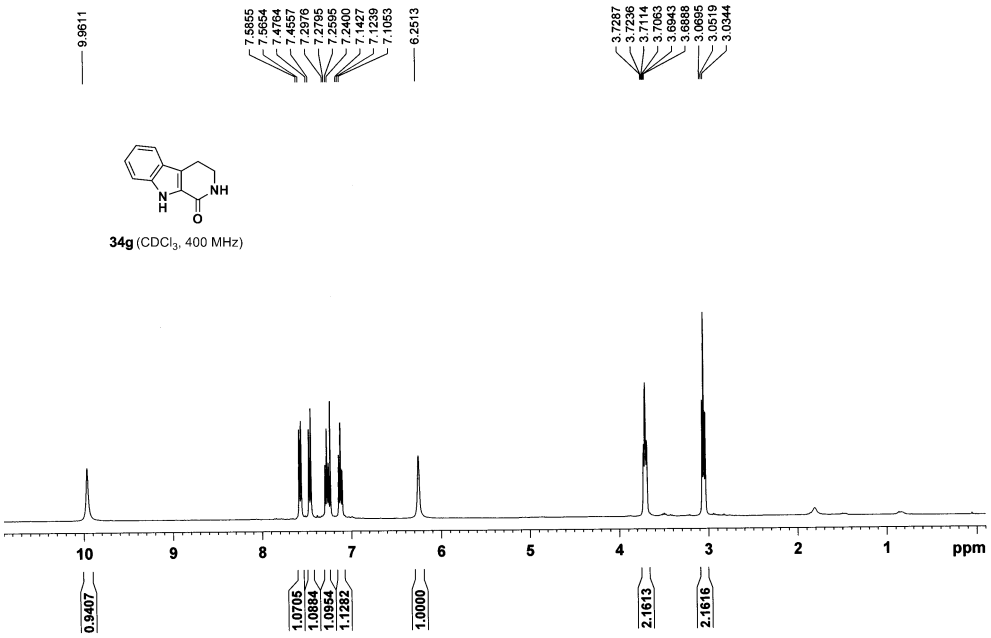


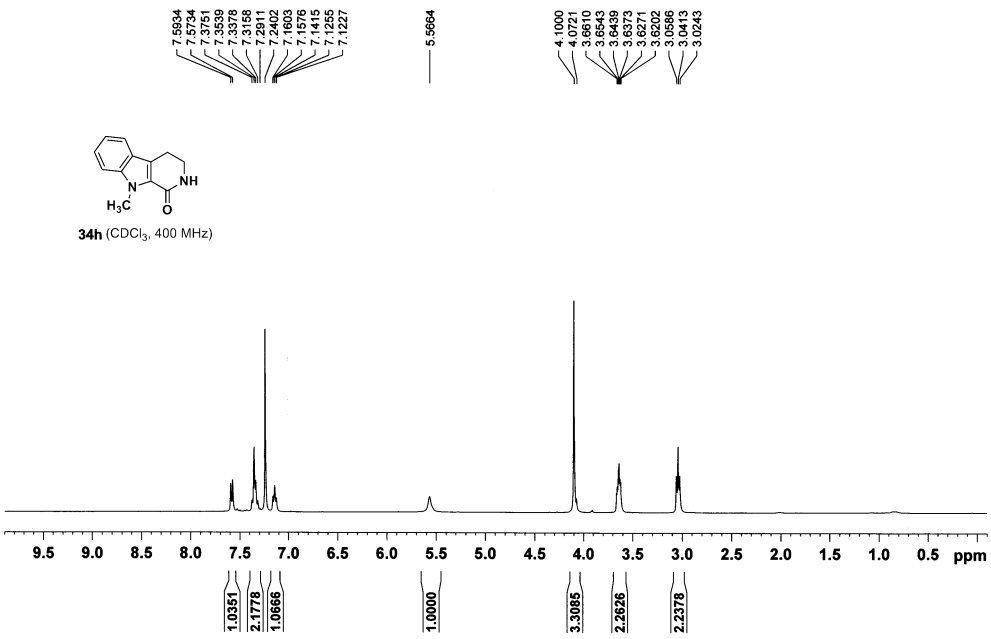
- ^{1}H NMR spectrum of compound **34c** and **34d**



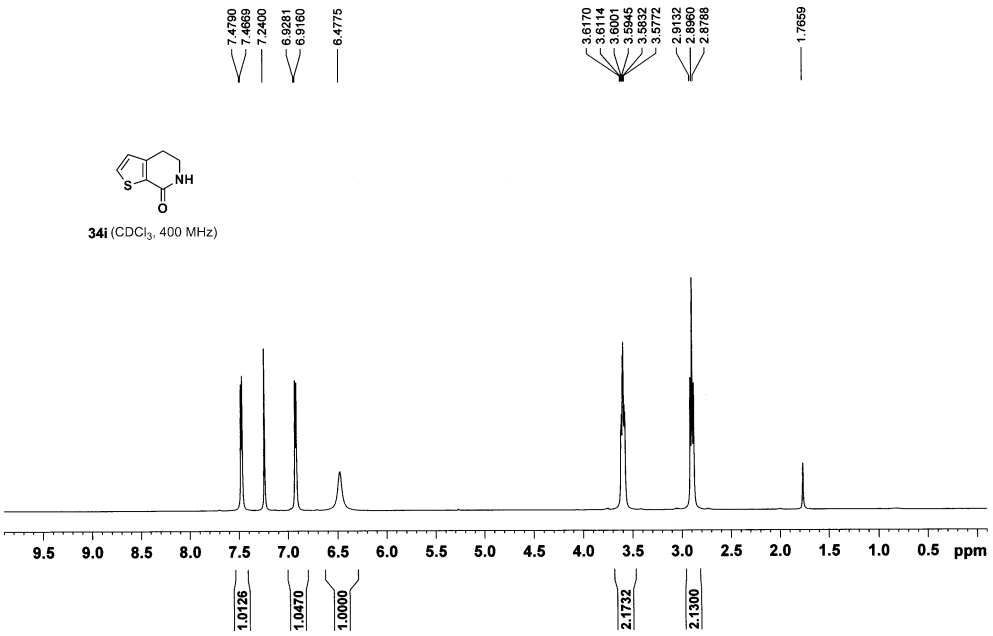


- ^{1}H NMR spectrum of compound **34g** and **34h**

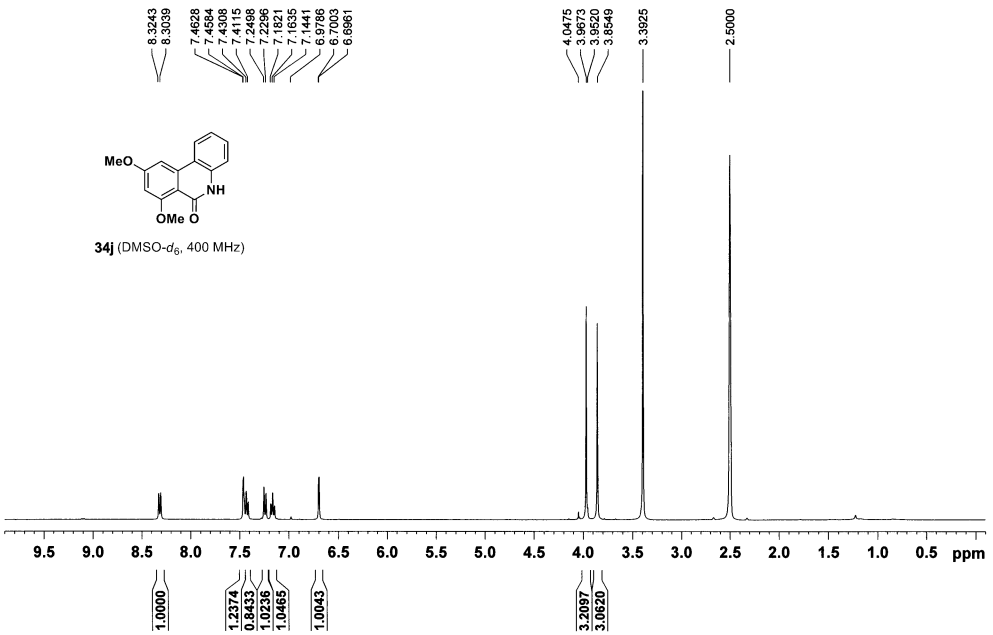




- ^{1}H NMR spectrum of compound **34i** and **34j**

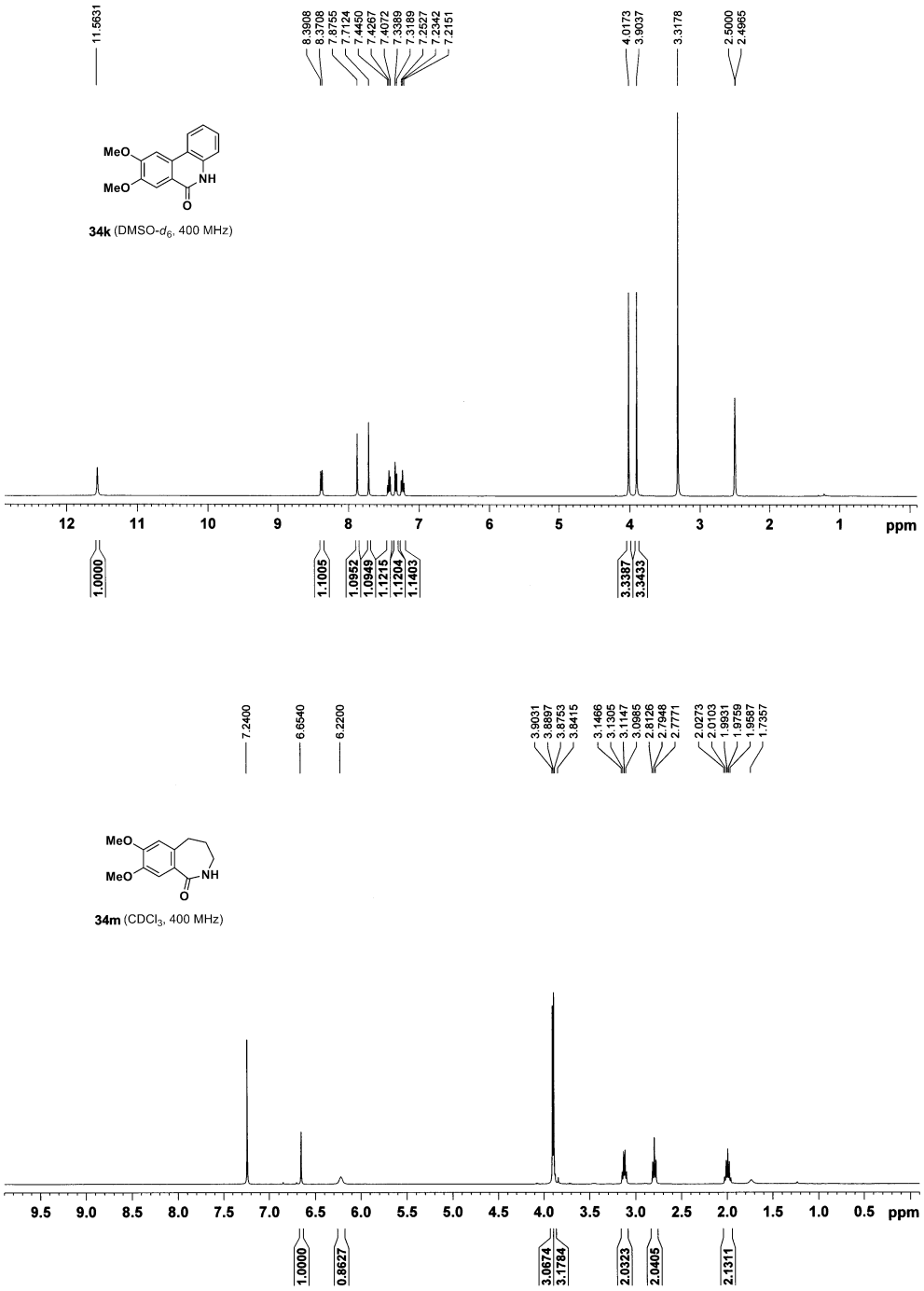


34i ($CDCl_3$, 400 MHz)



34j (DMSO-d_6, 400 MHz)

- ^{1}H NMR spectrum of compound **34k** and **34m**



Appendix II.

Publication List

(1) Cho, Jihee; Lee, Seokwoo; Hwang, Soonho; Kim, Sang Hoon; Kim, Jong Seung; Kim, Sanghee. "Calix[2]triazole[2]arenes; A Class of Hybrid Heterocalixarenes" *Eur. J. Org. Chem.* **2013**, 4614.

(2) In, Jinkyung[‡]; Hwang, Soonho[‡]; Kim, Changhun; Seo, Jae Hong; Kim, Sanghee. "Synthesis of 3,4-Dihydroisoquinolin-1-ones from *N*-Boc-(β-Arylethyl)-carbamates via Isocyanate Intermediates" *Eur. J. Org. Chem.* **2013**, 965. ([‡] These two authors contributed equally to this work.)

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국 문 초 록

(+)-*trans*-Dihydronarciclasine은 Amaryllidaceae isocarbostyril 알칼로이드 계열에 속하는 대표적인 화합물로서 다양한 암세포주에 대해 강력하고 선택적인 항암활성을 보인다고 알려져 있다.

본 논문은 쉽게 이용 가능한 시작물질로부터 매우 입체선택적이며 효과적인 합성법으로 (+)-*trans*-dihydronarciclasine의 비대칭 전합성을 수행하는 과정에 대해 제시하는 논문이다.

광학적으로 순수한 시작물질인 allylic alcohol은 cross-coupling 반응과 효소에 의한 광학분할 방법을 이용해 얻을 수 있었으며, 본 합성의 핵심 중간체인 vinylogous ester는 allylic ester로부터 amino acid ester-enolate Claisen rearrangement와 위치선택적인 Wacker oxidation, Dieckmann 축합반응을 통해 합성할 수 있었다. 이로부터 입체선택적인 산화-환원 반응을 거쳐 원하는 입체화학을 갖는 C-ring을 합성할 수 있었다.

특히 B-ring의 합성은 *N*-Boc carbamate로부터 합성된 isocyanate 중간체를 통한 Friedel-Crafts-type 고리화 반응을 통해, 기존에 본 계열 천연물의 합성에 많이 이용되는 Bischler-Napieralski 반응을 통한 고리화 반응의 낮은 선택성 문제를 해결하면서 효과적으로 수행할 수 있었다. 이 과정에서 얻어진 반응 조건은 다양한 3,4-dihydroisoquinolinone 및 관련된 heterocycle의 화합물 합성에도 응용 가능함을 확인하였다.

주요어: Acid-mediated cyclization, Antitumor agents, Ireland-Claisen rearrangement, Natural products, Total synthesis

학 번: 2007-21826

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藥學博士 學位論文

강력한 항암 활성 Isocarbostyril 알칼로이드인 (+)-*trans*-Dihydronarciclasine의 입체선택적 전합성

Stereoselective Total Synthesis of (+)-*trans*-Dihydronarciclasine, a Potent Anticancer Isocarbostyril Alkaloid

2014년 2월

서울大學校 大學院

製藥學科 藥品化學 專攻

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指導敎授 金 相 熙

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2014年 **2**月

서울大學校 大學院

製藥學科 藥品化學 專攻

黃 淳 浩

黃 淳 浩의 藥學博士 學位論文을 認准함

2014年 **2**月

委 員 長 _____ **(印)**

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Abstract

We have achieved a highly stereoselective and efficient total synthesis of *trans*-dihydronarciclasine from a readily available chiral starting material. Our scheme defines two of the five stereogenic centers of the natural product by an amino acid ester-enolate Claisen rearrangement. The other three stereogenic centers are created in a highly stereocontrolled fashion via a six-membered-ring vinylogous ester intermediate, which is generated from the γ,δ-unsaturated ester functional group of Claisen rearrangement product in an efficient three-step sequence. This concise total synthesis exemplifies the use of a highly regioselective Friedel-Crafts-type cyclization to form the B-ring via an isocyanate intermediate derived from an *N*-Boc group, which is superior to the conventional method using an imino triflate intermediate. This mild and regioselective reaction conditions are also applicable for synthesis of various substituted isoquinolin-1-ones, β-carbolines, thiophen fused ring systems and tetrahydrobenzoazepin-1-ones. Acid additives, such as $BF_3 \cdot Et_2O$, extend the application of the method to substrates bearing less nucleophilic aryl moieties by enhancing the Friedel-Crafts-type cyclization of isocyanate intermediates.

Key word: Acid-mediated cyclization, Antitumor agents, Ireland-Claisen rearrangement, Natural products, Total synthesis

Student Number: 2007-21826

Contents

I. Introduction

Based on their potent and selective anticancer activity as well as their unique structural features, *Amaryllidaceae* isocarbostyril alkaloids have been an attractive synthetic target for the last two decades.[1,2] Some representative members of this class of natural products are *trans*-dihydronarciclasine (**1**, Figure 1), pancratistatin (**2**), lycoricidine (**3**), and narciclasine (**4**). These natural isocarbostyrils exhibit potent cytotoxicity in the NCI 60 human tumor cell line panel with GI_{50} values in the nanomolar range.[3] Although *trans*-dihydronarciclasine has far greater anticancer activity than the intensively investigated pancratistatin (**2**) and other congeners,[3b] less effort has been devoted to biological and synthetic studies on *trans*-dihydronarciclasine until recently.[4]

The isolation of (+)-**1** from the Chinese medical plant *Zephyranthes candida* was reported in 1990.[5] Interestingly, it was produced synthetically long before its isolation from natural sources, through hydrogenation of narciclasine (**4**) with low diastereoselectivity.[6] The first total synthesis of the racemate was reported by Cho in 2007,[4a] which involved a Diels-Alder cycloaddition of 3,5-dibromo-2-pyrone for the preparation of functionalized C-ring. The first enantioselective synthesis by Studer appeared in 2008,[4b] in which the required absolute stereochemistry of C-ring was introduced by a Cu-catalyzed enantioselective nitroso Diels-Alder reaction. Both syntheses employed Banwell's modified Bischler-Napieralski reaction at a late stage of the sequence for closure of the B-ring.

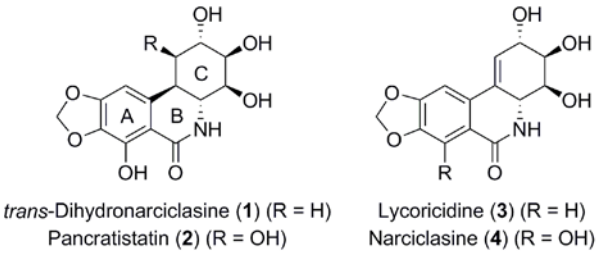


Figure 1. Chemical structures of compounds **1**−**4**.

Herein, we wish to describe a short and highly stereocontrolled total synthesis of (+)-**1** by a strategy that is unique as compared to other previous syntheses of *Amaryllidaceae* isocarbostyril alkaloids. Our route is characterized by the use of an *N*-Boc group first to steer the stereochemical course of a Claisen rearrangement, and then to generate an isocyanate intermediate for a highly regioselective Friedel-Crafts-type B-ring cyclization. This approach is superior to using the conventional Bischler-Napieralski-type B-ring cyclization, especially in the sense of regioselectivity.

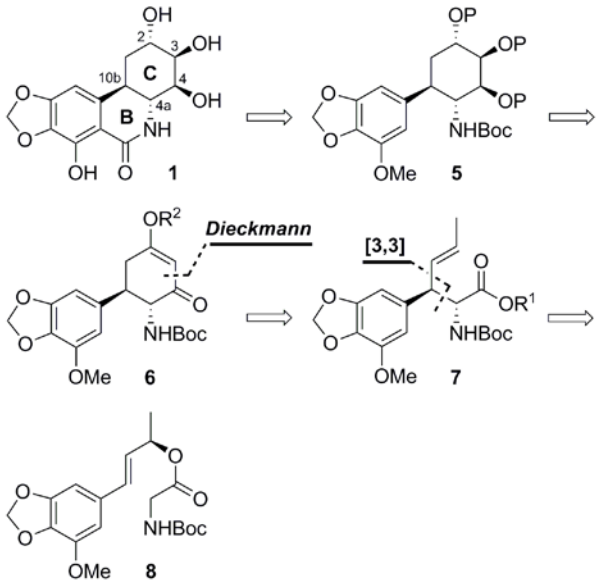
II. Results and Discussion

II-1. Retrosynthetic Analysis

As shown in Scheme 1, we planned to construct the B-ring of **1** at a late stage of the synthesis, similarly to many other *Amaryllidaceae* isocarbostyril synthetic approaches. We envisioned construction of the B-ring could be achieved by utilizing the *N*-Boc carbamate group in **5**, where this group is also essential for attaining high stereocontrol in the subsequent transformations (*vide infra*). Our strategy was premised on the selective transformation the *β*-keto enol ether function of **6** to the three contiguous hydroxyl groups in the C-ring of **5**. We expected that cyclic vinylogous ester **6** could be obtained regioselectively from the *γ*,*δ*-unsaturated ester **7** via regioselective Wacker oxidation, Dieckmann condensation, and regioselective vinylogous ester formation. We further envisioned that an ester enolate Claisen rearrangement of the Boc-protected amino acid allylic ester **8** would provide the γ,δ-unsaturated *α*-amino ester **7**.[7] In this transformation, the required stereochemistry of the two contiguous stereocenters at C-4a and C-10b could be installed with chirality transfer from a preformed chiral center in substrate **8** via a chair-like transition state. The Boc group was chosen as the amino protecting group because the stereoselectivity of ester enolate Claisen rearrangements of Boc-protected amino esters is generally superior to that of other carbamate-protected amino esters.[8] In addition, the bulkiness of the Boc group was expected to promote high reaction

selectivity through steric interactions or conformational reinforcement, especially in the introduction of the three contiguous hydroxyl group stereocenters.

Scheme 1. Retrosynthetic analysis of *trans*-dihydronarciclasine (**1**).



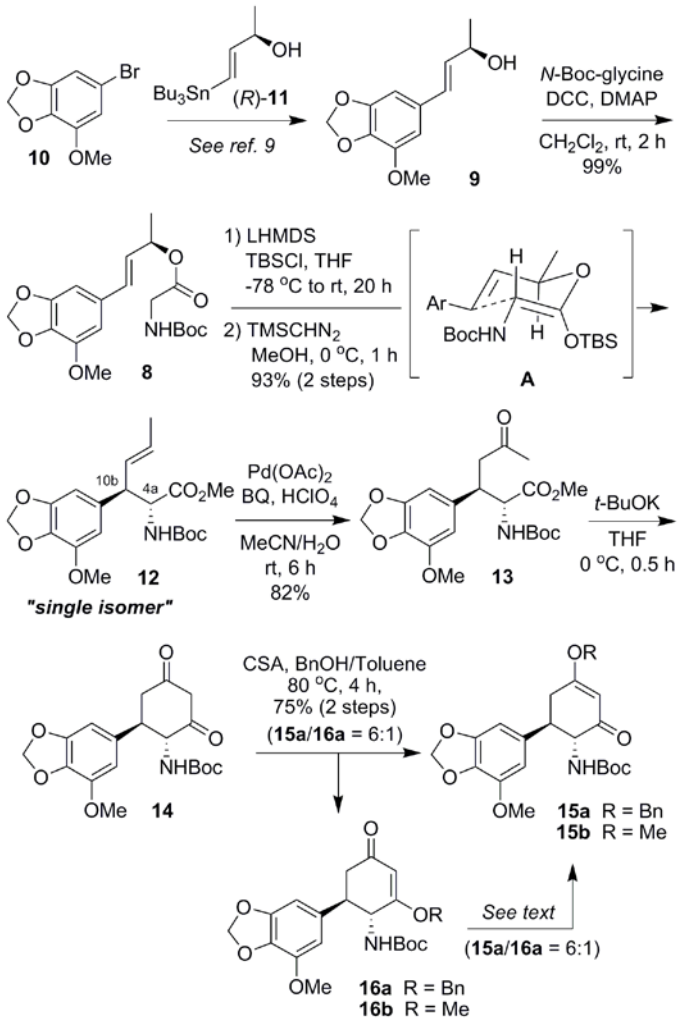
II-2. A-C Ring System Synthesis

As illustrated in Scheme 2, the synthesis was initiated by preparing Claisen substrate **8** from the enantiomerically enriched allylic alcohol **9**. The synthesis of **9** from the aryl bromide **10** and chiral building block (*R*)-**11** (>99% *ee*) was previously reported by us in

the total synthesis of **2**.[9] Allylic alcohol **9** was then coupled with *N*-Boc-glycine to provide the chiral allylic amino acid ester **8**. After some experimentation, we identified conditions that led to the formation of the desired rearranged product **12** in excellent stereoselectivity and yield. Deprotonation of **8** at −78 °C with LHMDS in THF in the presence of TBSCl resulted in the formation of the intermediate (*Z*)-silyl ketene acetal, which underwent Claisen rearrangement upon gradual warming to room temperature to afford **12** (93%) after treatment with TMS-diazomethane.[10] A single diastereomer was observed by NMR and HPLC analysis. The absolute configurations of the two new stereocenters were assumed to be 4a*R* and 10b*R* by invoking chair transition state **A** for the rearrangement, and these configurations were ultimately confirmed through conversion to the final natural product.

Efforts were next directed toward forming the C-ring by a two-step process that began with regioselective oxidation of the internal olefin to afford methyl ketone **13**. The resulting intermediate could then undergo Dieckmann condensation to give cyclic *β*-diketone **14**. In the event, highly regioselective (8:1) Wacker oxidation of olefin **12** could be achieved in 82% yield with $Pd(OAc)_2$ and benzoquinone (BQ).[11] Condensation of **13** using *t*-BuOK in THF provided the desired *β*-diketone **14**, which was used directly in the next step without further purification.[12]

Scheme 2. Synthesis of intermediate **15**.



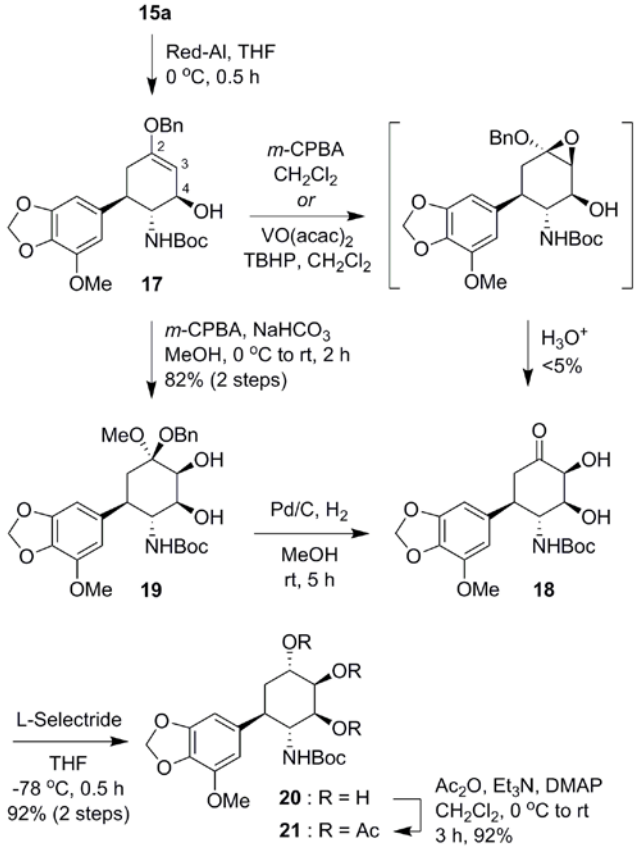
II-3. C-Ring Functionalization

Our approach to functionalize the C-3 position was to convert cyclic β-diketone moiety

of **14** to the corresponding vinylogous ester by enol etherification. The regiochemical outcomes of etherification of asymmetric cyclic *β*-diketones are often difficult to predict, and mixtures of the two possible products are frequently produced.[13] However, we envisioned that enol etherification of **14** would be regioselective under thermodynamic conditions, since vinylogous ester **15** was expected to be thermodynamically more stable than its regioisomer **16** primarily due to the lower steric strain. Some support was obtained from our computational modeling studies, which predicted that **15b** would be more stable than **16b** by 1.36 kcal/mol.[14] As expected, treatment of crude **14** with benzyl alcohol and a catalytic amount of camphorsulfonic acid in toluene at 80 °C led to the selective formation of vinylogous benzyl ester **15a** (64% yield from **13**), along with a minor amount of its regioisomer **16a** (6:1). **16a** could be recycled by chromatographic separation followed by resubjection to the above etherification conditions to isomerize it back to the 6:1 mixture in favor of **15a**.[15]

Next, our study focused on the selective conversion of the *β*-keto enol ether function of **15a** into a triol (Scheme 3). First, the carbonyl group of **15a** was stereoselectively reduced with Red-Al to give exclusively the required 4*β*-hydroxy group. Since allylic alcohol **17** was unstable,[13c,16] it was immediately used in the next step without chromatographic purification. Dihydroxylation of the enol ether **17** under the Upjohn dihydroxylation conditions (OsO_4, NMO)[17] afforded exclusively the undesired C3-*α* stereoisomer (79% from **15a**) instead of **18**. Even under the hydroxy-directed dihydroxylation conditions of Donohoe,[18] the same undesired isomer was formed (76%).

Scheme 3. Introduction of the stereocenters in the C ring.



On the other hand, epoxidation of the enol ether **17** by using *m*-CPBA or $VO(acac)_2$/TBHP system[19] did occur on the desired β-face of the molecule to produce the α-hydroxy ketone **18** with the desired C3 stereochemistry, but in a disappointingly low yield (<5%). To overcome the problem of low yield, the domino epoxidation-methanolysis protocol was employed.[20] Epoxidation with *m*-CPBA in MeOH in the presence of $NaHCO_3$ provided mixed ketal **19** as a single diastereoisomer in 82% yield (2 steps) from **15a**. Since α-hydroxy ketals are prone to rearrange under acidic conditions,[21]

the deketalization of **19** was effected gently by catalytic hydrogenation of the benzyl group to give ketone **18**. Dihydroxyketone **18** itself was also found to be unstable,[22] and readily decomposed to unidentified polar material. Thus, the best approach was to treat crude ketone **18** directly with the sterically demanding L-Selectride to give triol **20** as the sole stereoisomer in 92% overall yield from **19**.[23] Triol **20** was then protected to give triacetate **21** (92%).

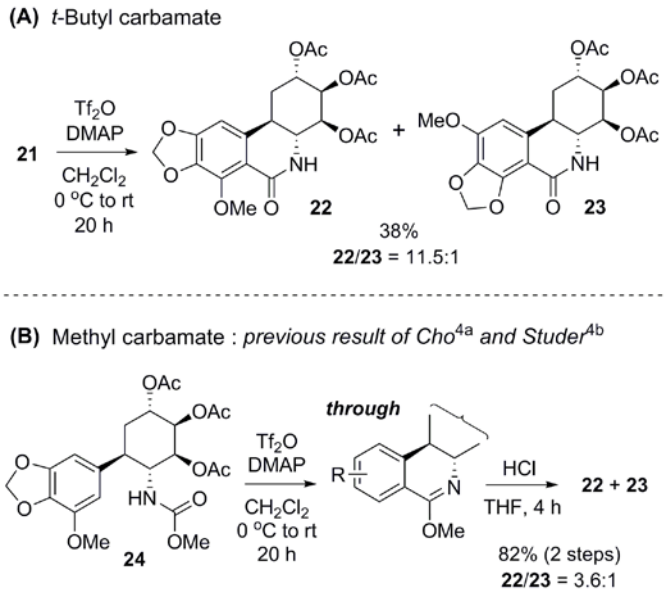
II-4. B-Ring Construction under Banwell's Modified Bischler-Napieralski Reaction Conditions

After completing the functionalization of the C-ring, we turned our attention to the construction of the B-ring to complete the total synthesis. Banwell's modified Bischler-Napieralski reaction,[24] which is thought to proceed via an imino triflate intermediate, has been used widely for closure of the B-ring in the synthesis of *Amaryllidaceae* alkaloids including *trans*-dihydronarciclasine (**1**) and pancratistatin (**2**). However, literature examples of this reaction show it only to be effective for primary alkyl carbamate substrates.[2c-e] Thus, we were uncertain at that time that the Banwell procedure would be applicable to B-ring formation using the *N*-Boc group in our case.

Under the standard Banwell's reaction conditions (Tf_2O/DMAP = 5/3 molar ratio, 0 °C), we were able to obtain the desired cyclization product **22** along with a minor amount of

the regioisomer **23** from the *N*-Boc carbamate **21**, but in a very low yield (38%) (Scheme 4). Interestingly, although the chemical yield was much lower (38% vs. 82%), the degree of regioselectivity in the B-ring formation was considerably higher than in the reported case in which Banwell's modified Bischler-Napieralski reaction conditions were applied to the corresponding methoxycarbonyl compound **24** (11.5:1 vs. up to 3.6:1).[4a,b] This remarkable regioselectivity difference between the cyclization of substrate **21** and **24** under the same reaction conditions implied that the two cycloaddition reactions might proceed via different intermediates.

Scheme 4. B-ring construction under Banwell's reaction conditions.



Recently, Schofield and co-workers have observed that upon treatment with 2.0 equiv of

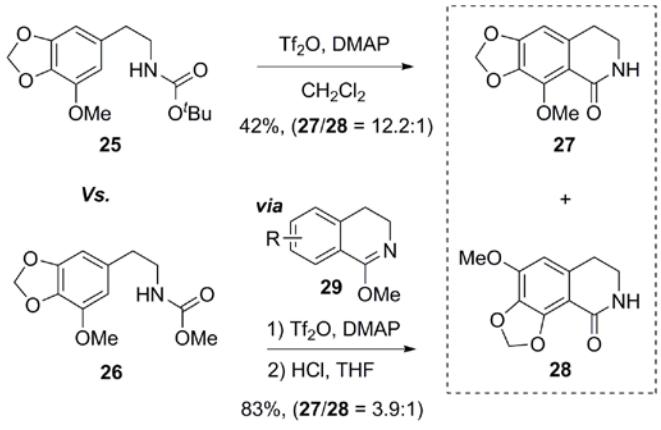
Tf_2O and 2.2 equiv of Et_3N or pyridine, *N*-Boc protected phenylalanine ester underwent dimerization to form a urea, most probably via an isocyanate intermediate.[25] This observation suggested the possibility that under Banwell's acidic reaction conditions, the *N*-Boc carbamate of **21** was converted to an isocyanate through loss of its acid-labile *t*-butyl group and dehydration, and this in situ generated isocyanate underwent intramolecular Friedel-Crafts-type cyclization. Although there have been several reports of isocyanates being used in Friedel-Crafts-type cyclization,[26] no examples of the intramolecular Friedel-Crafts capture of an isocyanate intermediate generated from *N*-Boc carbamates have been reported.[27] Isocyanates could be prepared by several methods, such as from an amine by treatment with phosgene[26a] or its equivalent including $(Boc)_2O$/DMAP,[26b] from an acid or amide utilizing Curtius or Hoffmann rearrangement,[26c,d] and from a carbamate by treatment with dehydrating reagents.[28] However, only a few examples of the direct conversion of *N*-Boc carbamate to an isocyanate have been reported.[28a,b]

II-5. Model studies and Optimization of B–Ring Construction

Based on the observation of Schofield and our initial results under Banwell's reaction conditions, our studies began with the reagent combination of Tf_2O and base for Friedel-Crafts-type reactions of *N*-Boc carbamate substrates via isocyanate intermediateds. *N*-Boc

carbamate **25** (Scheme 5) was chosen as an initial model substrate. Before identifying the optimal reaction conditions for our purposes, we first examined the chemical behavior differences between *N*-Boc carbamate substrate **25** and the corresponding *N*-Moc substrate **26** under Banwell's modified Bischler-Napieralski reaction conditions (Scheme 5). Under the Banwell conditions, *N*-Boc substrate **25** provided dihydroisoquinolinone **27** along with the minor regioisomeric product **28** in 42% combined yield and 12.2:1 regioselectivity. On the other hand, the *N*-Moc substrate **26** provided a methyl imidate **29**, which upon hydrolysis with 3 M HCl afforded **27** and **28** in a higher combined yield (83%) but with much lower regioselectivity (3.9:1). These results are very similar to those observed for the corresponding, more complex substrates **21** and **24**.

Scheme 5. Model Studies of B-ring Construction

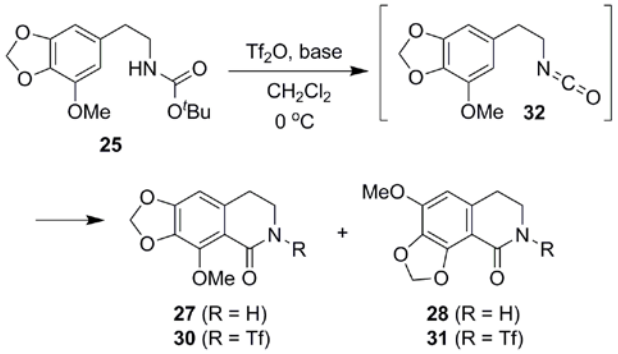


When DMAP in Banwell's reagent combination was replaced by the less basic pyridine and 2-chloropyridine,[29] *N*-Boc carbamate **25** provided **27** and **28** as well as their *N*-

triflated derivatives **30** and **31** (Table 1, entries 2 and 3). The combined yield of cyclized products was increased, and the high regioselectivity was maintained (entries 2 and 3 vs. entry 1). To avoid the *N*-triflation caused by excess Tf_2O,[30] the amount of Tf_2O was reduced to 1.5 equiv. In this case, isocyanate **32** was rapidly formed (within 20 min) as the only detectable reaction product and exhibited prolonged stability without conversion into dihydroisoquinolinones (entry 4). The identification of isocyanate **32** strengthened our belief that an *N*-Boc carbamate substrate could be transformed into a dihydroisoquinolinone via an isocyanate intermediate. The addition of excess Lewis acid (10 equiv) to the reaction mixture containing isocyanate **32** to facilitate the Friedel-Crafts reaction led to the formation of dihydroisoquinolinones **27** and **28** without the formation of the *N*-triflated derivatives (entries 5, 6, and 7). The yields from this stepwise process were much improved compared to that under the Banwell conditions (85–90% vs. 42%), although the degree of regioselectivity was slightly lower (8.5:1–9.7:1 vs. 12.2:1).

The above results implied that the reaction process was greatly influenced by the amount of base present and the acidity of the reaction medium. By further changing the molar ratios of Tf_2O and 2-chloropyridine, we finally determined the optimal reaction conditions for **25** to be 1.1 equiv of Tf_2O, 1.5 equiv of 2-chloropyridine and heating at 35 ^oC for 20 h. Under these conditions, *N*-triflation was minimized, and the product **27** was obtained in high yield and with high regioselectivity (entry 8).

Table 1. Optimization of Friedel-Crafts-type cyclization[a]



Entry	Tf_2O (eq)	Base (eq)	Lewis acid	*t* (h)	Yield (%)[b,c]	(**27**+**30**): (**28**+**31**)[d]
1	5.0	DMAP (3.0)	–	20	42	12.2:1
2	5.0	Py (3.0)	–	20	21+(45)	12.1:1
3	5.0	2-ClPy (3.0)	–	20	44+(40)	12.4:1
4	1.5	2-ClPy (3.0)	–	20	–	–
5[e]	1.5	2-ClPy (3.0)	$BF_3{\cdot}Et_2O$	2	86	8.5:1
6[e]	1.5	2-ClPy (3.0)	MsOH	0.5	90	8.5:1
7[e]	1.5	2-ClPy (3.0)	TfOH	0.5	85	9.7:1
8[f]	1.1	2-ClPy (1.5)	–	20	82	12.3:1

[a]Reaction conditions: **25** (0.3 mmol), Tf_2O, base, CH_2Cl_2 (10 mL), 0 ºC for 0.5 h and then rt. [b]Isolated yield of the mixture of **27** and **28**. The values in parentheses are the isolated yield of the mixture of **30** and **31**. [c]Each regioisomer could be separated. [d]Determined by ^1H NMR analysis. [e]Lewis acid was added after the formation of isocyanate. [f]Reaction was conducted at –78 ºC for 0.5 h and then at 35 ºC for 20 h.

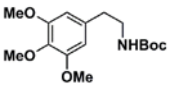
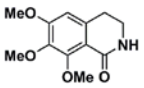
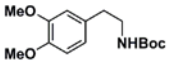
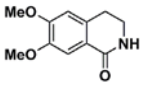
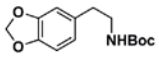
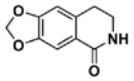
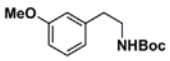
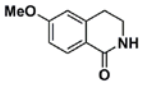
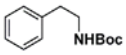
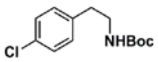
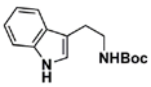
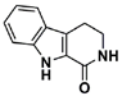
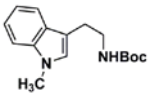
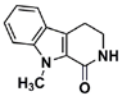
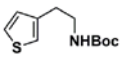
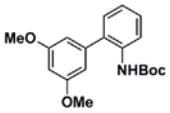
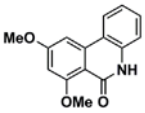
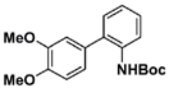
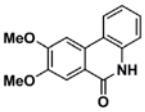
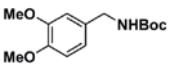
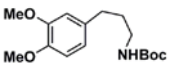
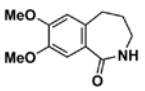
Using the optimized reaction conditions with or without an acid additive, we next investigated the scope of substrates (Table 2). All substrates were first subjected to the reaction conditions without an acid additive (Method A: Tf_2O (1.1 equiv), 2-ClPy (1.5 equiv), –78 ºC to rt). If method A gave unsatisfactory results, the Lewis acid was added

after the formation of isocyanate to facilitate the Friedel-Crafts reaction (Method B: Tf_2O (1.1 equiv), 2-ClPy (1.5 equiv), then $BF_3 \cdot Et_2O$ (5.0 equiv), –78 ºC to rt). The results are summarized in Table 2. Remarkably, the cyclizations of all compounds bearing electron-rich aryl rings proceeded in high yield and with high or exclusive regioselectivity.

The *N*-Boc carbamate **33a** bearing a trimethoxy-substituted benzene ring as a nucleophilic moiety was easily transformed to 3,4-dihydroisoquinolin-1-one **34a** using method A in 71% yield (entry 1). The 3,4-dimethoxy substituted substrate **33b** also afforded the cyclized product **34b** in high yield (87%) using method A with very high regioselectivity (>20:1) (entry 2). However, substrates **33c** and **33d** required the addition of $BF_3 \cdot Et_2O$ for cyclization (entries 3 and 4) to give products. High yield and regioselectivity were also observed. The Lewis acid requirement for these substrates might be due to the lower nucleophilicity of their aryl ring moieties compared to that of the electron-rich substrates **33a** and **33b**.[31] Substrates with electron-deficient or neutral groups at the aryl moiety did not undergo the cyclization reaction under either set of reaction conditions, yielding only the corresponding isocyanates (entries 5 and 6).

The phenyl rings could also be replaced by heteroarene units. Electron-rich heterocycles, such as indole and *N*-methyl indole moieties, showed good cyclization efficiency to afford tetrahyrdo-*β*-carbolin-1-ones **34g** and **34h** in good yield (70% and 92%, respectively) (entries 7 and 8). With the aid of an acid additive, thiopen substrate **33i** also produced the cyclized product **34i** in 79% yield (entry 9).

Table 2. Substrate Scope of the Reactions

Entry	*N*-Boc carbamate (**33**)		Product (**34**)		Method[a]	Yield[b] (%)
1	**33a**		**34a**		A	71
2	**33b**		**34b**		A	87
3	**33c**		**34c**		B	86
4	**33d**		**34d**		B	83[c]
5	**33e**		**34e**	-	A or B	-[d]
6	**33f**		**34f**	-	A or B	-[d]
7	**33g**		**34g**		A	70
8	**33h**		**34h**		A	92
9	**33i**		**34i**		B	79
10	**33j**		**34j**		A	81
11	**33k**		**34k**		B	70
12	**33l**		**34l**	-	A or B	-[d]
13	**33m**		**34m**		B	83[e]

[a]Method A: Tf_2O (1.1 equiv), 2-ClPy (1.5 equiv), CH_2Cl_2, –78 ºC to rt. Method B: Tf_2O (1.1 equiv), 2-ClPy

(1.5 equiv), $BF_3 \cdot Et_2O$ (5.0 equiv), CH_2Cl_2, –78 ºC to rt. [b]Isolated yield. [c]Regioisomeric mixture (18:1). [d]Lactam product was not detected. [e]TfOH was used instead of $BF_3 \cdot Et_2O$.

The substrate for which the *N*-Boc carbamate group is bonded directly to an aromatic ring also provided the cyclized product (entries 10 and 11). The 3,5-dimethoxy substituted substrate **33j** smoothly afforded phenanthridone **34j** in high yield (81%) under method A. However, the 3,4-dimethoxy substituted substrate **33k** required the addition of the Lewis acid for cyclization and provided phenanthridone **34k** in a slightly lower yield (70%).

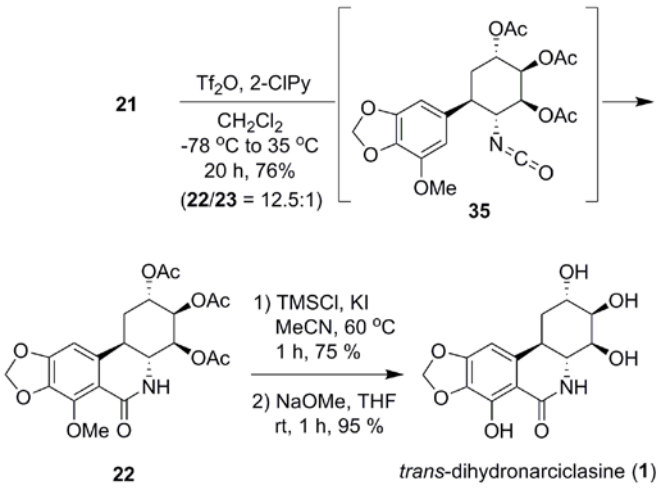
We also explored the feasibility of forming a five- or seven-membered ring lactam using these methods. Attempts to generate the dihydro-isoindolone **34l**, from the reaction of substrate **33l** under the above conditions produced complicated unidentified mixtures (entry 12).[32] However, under acid-induced conditions, *γ*-arylpropylcarbamate **33m** could be transformed into the benzo[*c*]azepin-1-one **34m** in 83% yield (entry 13).

II-6. Final Stages and Completion of the Synthesis

By applying these optimized conditions to *N*–Boc carbamate **21**, we were able to obtain the desired cyclization product **22** with very high regioselectivity (12.5:1) in 76% yield (Scheme 6). After careful monitoring of the reaction of **21**, we could identify a somewhat unstable isocyanate intermediate **35** and its identity was mainly confirmed by IR

spectroscopy (2253 cm^{-1}). The total synthesis was completed by demethylation with TMSCl/KI (75%) and removal of the acetate protecting groups with NaOMe (95%) to give (+)–**1**. The spectroscopic and optical rotation data of the synthetic material were in good agreement with those reported for the natural product.

Scheme 6. Completion of the total synthesis.



III. Conclusion

In conclusion, the total synthesis of (+)-*trans*-dihydronarciclasine (**1**) has been accomplished in 16% overall yield in a completely substrate-controlled manner from the readily accessible chiral starting material **9**. One of the unique features of this synthesis is the highly stereocontrolled introduction of the five contiguous stereogenic centers based on a single stereocenter in starting material. Two of the five stereocenters were defined by an Ireland-Claisen rearrangement, and the other three centers were created through diastereoselective reduction and oxidation reactions. The stereoselectivity for introducing all of the stereogenic reactions was excellent, with only a single diastereomer of each product being observed. The concise nature of this total synthesis hinges in part on the first demonstration of the successful conversion of a Claisen rearrangement product into a six-membered cyclic vinylogous ester via a regioselective Wacker oxidation and Dieckmann condensation based sequence. The successful B-ring formation with high regioselectivity from an *N*-Boc substrate via an isocyanate intermediate is also quite noteworthy, and the present transformation is a useful complement to Banwell's variant of the Bischler-Napieralski reaction in the synthesis of dihydroisocarbostyrils from *β*-arylethylcarbamates.

IV. Experimental

IV-1. General.

All chemicals were of reagent grade and used as received. All reactions were performed under an inert atmosphere of dry nitrogen using distilled dry solvents. Reactions were monitored by TLC analysis using silica gel 60 F-254 thin layer chromatography plates. Flash column chromatography was carried out on silica gel (230-400 mesh). Optical rotations were measured using sodium light (D line 589.3 nm). ^{1}H NMR (300, 400 or 500 MHz) and ^{13}C NMR (75, 100 or 125 MHz) spectra were recorded in δ units relative to the non-deuterated solvent as the internal reference. IR spectra were measured on a Fourier Transform Infrared spectrometer. Mass spectra (MS) and high resolution mass spectra (HRMS) were recorded using fast atom bombardment (FAB).

IV-2. Experimental procedure and spectroscopic data analysis

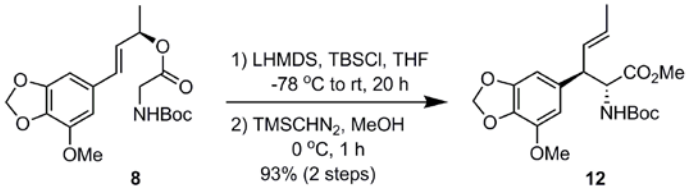
IV-2.1. All the compounds of the total synthesis process

(*R*,*E*)-4-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)but-3-en-2-yl 2-(*tert*-butoxycarbonyl amino)ace tate (8):

To a solution of allylic alcohol **9**[9] (3.50 g, 15.75 mmol, 1.0 equiv) in CH_2Cl_2 (80 mL) were added *N*-Boc-glycine (3.31 g, 18.90 mmol, 1.2 equiv), DMAP (383 mg, 3.15 mmol, 0.2 equiv), and DCC (3.90 g, 18.90 mmol, 1.2 equiv) at 0 °C. The reaction mixture was stirred for 2 h at room temperature followed by dilution with hexane. The generated white precipitate was removed by filtration through a pad of Celite and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc, 2:1) to give allylic amino acid ester **8** (5.91 g, 99%) as a pale yellow oil. $[\alpha]^{25}_{D}$ +84.7 (*c* = 2.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 6.5 Hz, 3H), 1.40 (s, 9H), 3.85 (s, 3H), 3.85−3.86 (m, 2H), 5.09 (br s, 1H), 5.50 (pent, *J* = 6.5 Hz, 1H), 5.90 (s, 2H), 5.96 (dd, *J* = 6.9, 15.8 Hz, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.48 (s, 1H), 6.55 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.25, 28.16 (3C), 42.56, 56.39, 72.15, 79.76, 99.99, 101.43, 106.90, 126.72, 130.91, 131.87, 135.18,

143.43, 149.02, 155.61, 169.57 ppm; IR ($CHCl_3$): υ_{max} = 3399, 2979, 1713, 1627, 1510, 1431, 1368 cm^{-1}; MS (FAB): *m/z*: 379 $[M]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{25}NO_7$: 379.1631 $[M]^+$; found: 379.1630.

(2*R*,3*R*,*E*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)hex-4-enoate (12):



To a stirred solution of ester **8** (5.00 g, 13.18 mmol, 1.0 equiv) in THF (80 mL) was added TBSCl (5.96 g, 39.54 mmol, 3.0 equiv) in THF (8 mL). After the mixture was cooled to –78 °C, LHMDS (1.0 m soln. in THF, 40 mL, 39.54 mmol, 3.0 equiv) was slowly added to the reaction flask over 30 min. The reaction mixture was slowly warmed to room temperature and stirred for 20 h. The reaction was quenched with saturated NH_4Cl solution at 0 °C, stirred for another 1 h at room temperature, and then the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to give the desired acid **12-acid** as a single isomer, which was used in the next step without further purification. A small amount of pure acid was isolated by column chromatography on silica gel (hexane/EtOAc, 2:1 + 1% AcOH) for ^1H NMR and HRMS analysis. ^1H NMR (400 MHz, CD_3OD): δ = 1.33 (s, 9H), 1.65 (d, *J* = 5.9 Hz, 3H), 3.52 (t, *J* = 8.6 Hz, 1H), 3.85 (s, 3H),

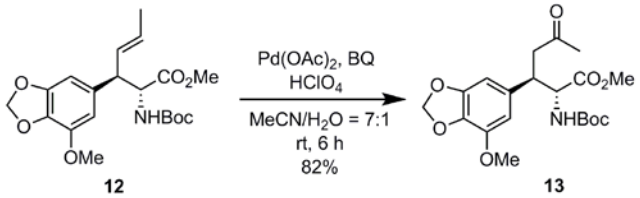
4.34 (d, *J* = 8.8 Hz, 1H), 5.50−5.58 (m, 1H), 5.60−5.67 (m, 1H), 5.86 (d, *J* = 3.4 Hz, 2H), 6.42 (s, 1H), 6.44 ppm (s, 1H); MS (FAB): *m/z*: 402 $[M+23]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{25}NO_7$: 379.1631 $[M]^+$; found: 379.1655.

The crude mixture obtained above was dissolved in MeOH (44 mL), and trimethylsilyl-diazomethane solution (2.0 m soln. in diethyl ether, 17 mL, 32.95 mmol, 2.5 equiv) was added dropwise, causing instantaneous bubbling, along with a change from colorless to yellow. After allowing the reaction to proceed for 1 h, the reaction was quenched with small amount of acetic acid, at which time gas evolved and the reaction mixture became colorless. The solvent was removed in vacuo, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc, 4:1) to give the desired ester **12** (4.82 g, 93% for 2 steps) as a pale yellow solid. $[\alpha]^{25}_D$ −45.2 (*c* = 0.88, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.38 (s, 9H), 1.67 (d, *J* = 5.1 Hz, 3H), 3.54−3.50 (m, 1H), 3.66 (s, 3H), 3.87 (s, 3H), 4.50 (t, *J* = 7.3 Hz, 1H), 4.78 (d, *J* = 7.6 Hz, 1H), 5.54−5.63 (m, 2H), 5.92 (s, 2H), 6.31 (s, 1H), 6.36 ppm (d, *J* = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.81, 28.02 (3C), 51.16, 51.71, 56.44, 57.76, 79.77, 101.23, 101.80, 107.36, 128.24, 128.87, 133.95, 134.10, 143.38, 148.88, 155.07, 172.02 ppm; IR ($CHCl_3$): υ_{max} = 3377, 2976, 1744, 1715, 1634, 1510, 1452 cm^{-1}; MS (FAB): *m/z*: 394 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{28}NO_7$: 394.1866 $[M+H]^+$; found: 394.1972.

The diastereomeric purity of ester **12** was determined by crude ^{1}H NMR spectrum analysis. The enantiomeric purity of ester **12** (>99%*ee*) was determined by chiral HPLC analysis (CHIRALCEL OJ-H, 2-propanol/hexane (0 to 10%, 60 min), flow rate: 0.5

mL/min, t_R: (chiral sample) = 37.7 min [(–)-isomer]; t_R (racemic sample) = 37.1 [(–)-isomer], 42.5 min [(+)-isomer], detected at 225 nm).

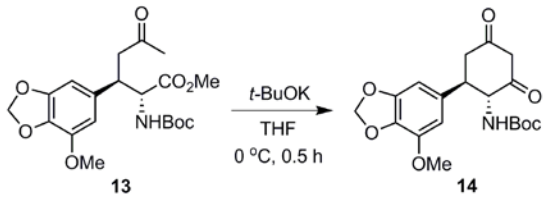
(2*R*,3*R*)-methyl 2-(*tert*-butoxycarbonylamino)-3-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-5-oxohexanoate (13):



To a mixture of $Pd(OAc)_2$ (685 mg, 3.05 mmol, 0.3 equiv) and 1,4-benzoquinone (1.10 g, 10.17 mmol, 1.0 equiv) in MeCN/H_2O (7:1, v/v, 51 mL) was added $HClO_4$ (1.0 m soln. in MeCN, 2.0 mL, 2.03 mmol, 0.2 equiv). The resulting solution was stirred 1 h at room temperature and ester **12** (4.00 g, 10.17 mmol, 1.0 equiv) was added to reaction flask. After being stirred for 6 h at room temperature, the reaction was quenched with saturated $NaHCO_3$ solution at 0 °C and then the mixture was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Due to similar R_f values for the hydroquinone generated and the product under various eluent conditions, hydroquinone was acetylated under standard conditions (Ac_2O, NEt_3, DMAP, CH_2Cl_2). The resulting crude mixture was purified by flash column chromatography on silica gel (hexane/EtOAc, 2:1) to give desired methyl ketone **13** (3.41 g, 82%) as a pale brown oil. $[\alpha]^{25}_D$ −55.3 (*c* = 0.72, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9H), 2.13 (s, 3H), 2.67 (dd, *J* = 5.4, 17.7 Hz, 1H), 2.98 (dd, *J* = 8.4, 17.8 Hz,

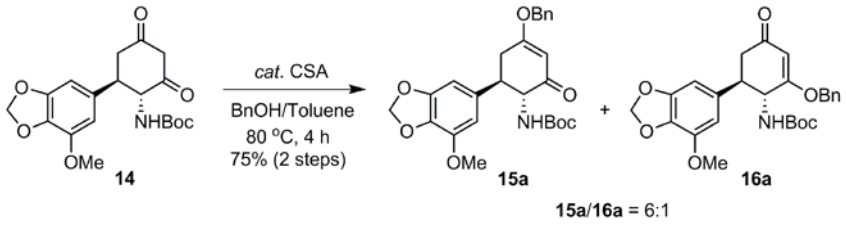
1H), 3.70 (s, 3H), 3.78 (br s, 1H), 3.86 (s, 3H), 4.60 (d, J = 5.0 Hz, 1H), 4.97 (d, J = 8.3 Hz, 1H), 5.92 (s, 2H), 6.26 (d, J = 1.3 Hz, 1H), 6.31 ppm (d, J = 1.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.14 (3C), 30.14, 42.25, 45.14, 52.10, 56.47, 56.58, 79.96, 101.31, 101.64, 108.10, 133.00, 134.46, 143.30, 148.94, 155.70, 171.40, 205.80 ppm; IR ($CHCl_3$): υ_{max} = 3381, 2978, 1714, 1633, 1510, 1452, 1435 cm^{-1}; MS (FAB): *m/z*: 409 $[M]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{27}NO_8$: 409.1737 $[M]^+$; found: 409.1749.

***tert*-butyl (1*R*,2*R*)-2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-4,6-dioxocyclohexyl carbamate (14):**



To a stirred solution of methyl ketone **13** (3.00 g, 7.33 mmol, 1.0 equiv) in THF (40 mL) was slowly added *t*-BuOK (1.0 m soln. in THF, 19 mL, 18.3 mmol, 2.5 equiv) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C, then quenched by addition of saturated NH_4Cl solution, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give β-diketone **14**.[12] The resulting white solid was used in the next step without further purification.

Vinylogous benzyl ester (15a and 16a):



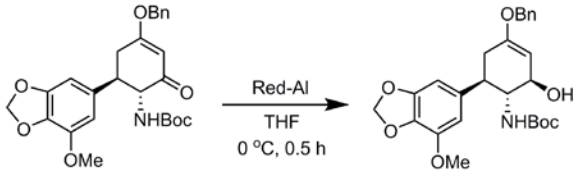
To a mixture of crude *β*-diketone **14** in toluene (30 mL) and benzyl alcohol (7.5 mL), catalytic 10-camphorsulfonic acid (170 mg, 0.73 mmol, 0.1 equiv) was added. The reaction mixture was stirred for 4 h at 80 °C and then quenched by the addition of NEt_3 (0.1 mL) at 0 °C. This was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give vinylogous benzyl ester **15a** (2.19 g, 64%) and minor isomer **16a** (377 mg, 11%) as white solids. The minor isomer **16a** could be cleanly separated chromatographically and be isomerized back to the 6:1 mixture (combined 70% yield) in favor of **15a** by resubjection to the above etherification conditions. Additional **15a** (226 mg) could be obtained from **16a** through this isomerization.

***Major isomer 15a* (*tert*-butyl (1*R*,6*R*)-4-(benzyloxy)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2-oxocyclohex-3-enylcarbamate):** $[\alpha]^{25}_{D}$ +21.6 (*c* = 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (s, 9H), 2.66 (dd, *J* = 4.7, 17.5 Hz, 1H), 2.81−2.89 (m, 1H), 3.21 (t, *J* = 8.6 Hz, 1H), 3.84 (s, 3H), 4.25−4.38 (m, 1H), 4.75−4.90 (m, 3H), 5.55 (s, 1H), 5.87 (d, *J* = 2.3 Hz, 2H), 6.42 (s, 1H), 6.45 (s, 1H), 7.29−7.36 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.01 (3C), 37.65, 45.95, 56.41, 59.58, 70.86, 79.30, 101.20,

101.70, 101.88, 107.20, 127.63 (2C), 128.48, 128.59 (2C), 134.11, 134.54, 134.59, 143.30, 148.65, 155.73, 174.82, 194.95 ppm; IR ($CHCl_3$): υ_{max} = 2977, 1708, 1665, 1608, 1514, 1453, 1364 cm^{-1}; MS (FAB): *m/z*: 468 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{26}H_{30}NO_7$: 468.2022 $[M+H]^+$; found: 468.2010.

***Minor isomer 16a* (*tert*-butyl (1*R*,6*R*)-2-(benzyloxy)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-4-oxocyclohex-2-enylcarbamate):** ^1H NMR (500 MHz, DMSO-d_6): δ = 1.25 (s, 9H), 2.36 (dd, *J* = 3.9, 16.1 Hz, 1H), 2.78 (dd, *J* = 13.4, 16.0 Hz, 1H), 3.29−3.39 (m, 1H), 3.80 (s, 3H), 4.66 (t, *J* = 9.9 Hz, 1H), 4.97−5.03 (m, 2H), 5.50 (s, 1H), 5.94 (s, 2H), 6.59 (s, 2H), 7.04 (d, *J* = 9.1 Hz, 1H), 7.33−7.39 ppm (m, 5H).

***tert*-butyl (1*R*,2*R*,6*R*)-4-(benzyloxy)-2-hydroxy-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)cyclohex-3-enylcarbamate (17):**

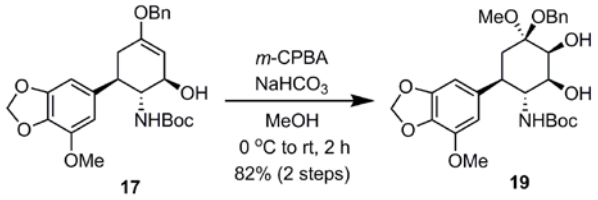


15a **17**

To a stirred solution of vinylogous benzyl ester **15a** (2.00 g, 4.28 mmol, 1.0 equiv) in THF (43 mL) was slowly added Red-Al (sodium bis(2-methoxyethoxy)aluminum dihydride (70% in toluene, ca. 3.6 m), 1.8 mL, 6.42 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred for additional 30 min, and then quenched by the addition of saturated NH_4Cl solution at 0 °C, and extracted twice with EtOAc. The combined organic

layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give allylic alcohol **17** as a single isomer.[33] Due to its instability under acidic conditions, the resulting pale yellow oil was used in the next step without further purification. The diastereomeric purity of alcohol **17** was determined by crude ^{1}H NMR spectrum analysis. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 2.40 (dd, *J* = 5.1, 16.8 Hz, 1H), 2.52 (t, *J* = 16.8 Hz, 1H), 2.89 (dt, *J* = 5.5, 11.5 Hz, 1H), 3.69 (td, *J* = 7.1, 11.8 Hz, 1H), 3.89 (s, 3H), 4.41 (br s, 2H), 4.67−4.90 (m, 3H), 5.90−6.00 (m, 2H), 6.38−6.44 (m, 2H), 7.27−7.42 ppm (m, 5H).

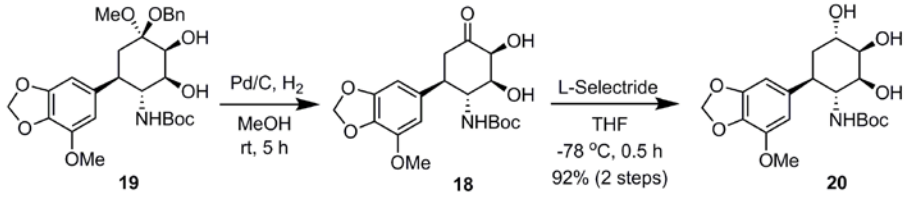
***tert*-butyl (1*R*,2*S*,3*S*,4*R*,6*R*)-4-(benzyloxy)-2,3-dihydroxy-4-methoxy-6-(7-methoxy benzo[*d*][1,3]dioxol-5-yl)cyclohexylcarbamate (19):**



To the crude mixture of allylic alcohol **17** obtained in the previous step in MeOH (22 mL) was added $NaHCO_3$ (1.08 g, 12.84 mmol, 3.0 equiv) and *m*-CPBA (1.11 g, 6.42 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred for 2 h at room temperature, and then quenched by addition of saturated $Na_2S_2O_3$ solution at 0 °C, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:2) to give ketal **19** (1.82 g, 82% for 2 steps from **15a**) as a

single isomer. $[\alpha]^{25}_{D}$ +11.8 (*c* = 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$ + D_2O): δ = 1.29 (s, 9H), 2.02 (dd, *J* = 2.0, 13.9 Hz, 1H), 2.12 (t, *J* = 13.9 Hz, 1H), 2.51 (dt, *J* = 3.5, 12.5 Hz, 1H), 3.27 (s, 3H), 3.73 (dd, *J* = 2.5, 9.8 Hz, 1H), 3.86 (s, 3H), 3.91 (br s, 1H), 4.13 (s, 1H), 4.38 (d, *J* = 7.9 Hz, 1H), 4.50 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.4 Hz, 1H), 5.90 (d, *J* = 3.2 Hz, 2H), 6.40 (d, *J* = 3.8 Hz, 2H), 7.26−7.38 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.07 (3C), 34.95, 43.21, 47.81, 54.94, 56.46, 62.33, 70.87, 73.64, 79.77, 100.99, 101.19, 101.97, 106.77, 127.33, 127.42 (2C), 128.26 (2C), 133.89, 135.89, 138.08, 143.49, 148.71, 157.19 ppm; IR ($CHCl_3$): υ_{max} = 3398, 2973, 1691, 1635, 1515 cm^{-1}; MS (FAB): *m/z*: 518 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{27}H_{36}NO_9$: 518.2390 $[M+H]^+$; found: 518.2377.

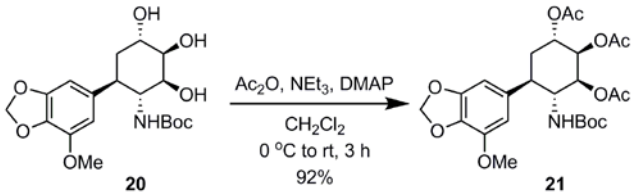
***tert*-butyl (1*R*,2*S*,3*R*,4*S*,6*R*)-2,3,4-trihydroxy-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)cyclohexylcarbamate (20):**



To a solution of **19** (1.50 g, 2.90 mol, 1.0 equiv) in MeOH (30 mL) was added 10% Pd/C (450 mg, 30% wt. of **19**). The flask was evacuated, filled with H_2, and stirred at room temperature for 5 h. After this, the reaction mixture was diluted with EtOAc, filtered through a pad of Celite, and concentrated in vacuo to give crude mixture of dihydroxyketone **18**. Due to its instability, resulting colorless oil was used in the next step

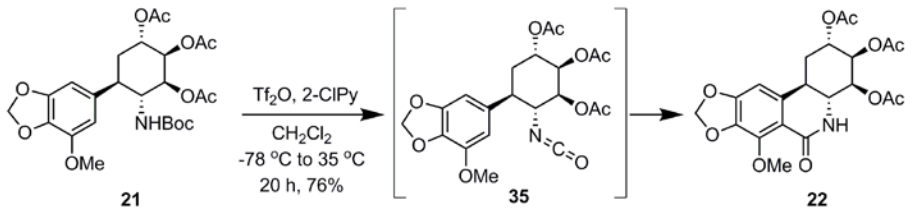
without further purification. To the crude mixture of **18** in THF (30 mL) was slowly added L-Selectride (lithium tri-*sec*-butylborohydride, 1.0 m soln. in THF, 4.4 mL, 4.35 mmol, 1.5 equiv) at −78 °C. The reaction mixture was stirred for 30 min at -78 °C, and then quenched by addition of saturated NH_4Cl solution at 0 °C, and extracted twice with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/Acetone, 1:2) to give triol **20** (1.06 g, 92% for 2 steps from **19**) as a single isomer. $[\alpha]^{25}_D$ +0.99 (*c* = 0.65, CH_3OH); ^1H NMR (400 MHz, CD_3OD): δ = 1.25 (s, 9H), 1.71 (d, *J* = 13.6 Hz, 1H), 2.10 (t, *J* = 13.2 Hz, 1H), 2.86 (t, *J* = 11.0 Hz, 1H), 3.34 (s, 1H), 3.70−3.78 (m, 1H), 3.81 (s, 1H), 3.85 (s, 3H), 3.95 (s, 2H), 5.80−5.86 (m, 2H), 6.44 (s, 1H), 6.49 ppm (s, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ = 29.47 (3C), 37.08, 44.65, 56.77, 57.89, 71.52, 73.56, 75.01, 80.34, 102.95, 103.98, 109.91, 135.68, 139.56, 145.36, 150.76, 159.41 ppm; IR (neat): υ_{max} = 3388, 2925, 1683, 1635, 1513 cm^{-1}; MS (FAB): *m/z*: 397 $[M]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{27}NO_8$: 397.1737 $[M]^+$; found 397.1753.

(1*S*,2*R*,3*S*,4*R*,5*R*)-4-(*tert*-butoxycarbonylamino)-5-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)cyclohexane-1,2,3-triyl triacetate (21):



To a mixture of triol **20** (700 mg, 1.76 mmol, 1.0 equiv) in CH_2Cl_2 (18 mL) was added NEt_3 (2.0 mL, 14.08 mmol, 8.0 equiv), DMAP (21.5 mg, 0.176 mmol, 0.1 equiv), and Ac_2O (0.84 mL, 8.81 mmol, 5.0 equiv) at 0 °C. After being stirred for 3 h at room temperature, the reaction was quenched by addition brine at 0 °C and then the mixture was extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1) to give triacetate **21** (848 mg, 92%) as a colorless oil. $[\alpha]^{25}_D$ +44.4 (*c* = 0.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (br s, 9H), 1.90−2.02 (m, 5H), 2.10 (s, 3H), 2.15 (s, 3H), 2.74−2.84 (m, 1H), 3.86 (s, 3H), 4.06−4.19 (m, 1H), 4.20−4.27 (m, 1H), 4.99 (d, *J* = 3.0 Hz, 1H), 5.13 (d, *J* = 9.8 Hz, 1H), 5.28 (s, 1H), 5.88 (d, *J* = 5.1 Hz, 2H), 6.36−6.42 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.69, 20.92, 21.01, 28.03 (3C), 33.76, 43.52, 52.12, 56.52, 68.83, 69.05, 71.17, 79.17, 101.27, 101.90, 107.02, 134.05, 135.01, 143.41, 148.81, 155.21, 169.20, 169.38, 170.53 ppm; IR ($CHCl_3$): υ_{max} = 3387, 2976, 1750, 1634, 1514 cm^{-1}; MS (FAB): *m/z*: 523 $[M]^+$; HRMS (FAB): *m/z* calcd for $C_{25}H_{33}NO_{11}$: 523.2054 $[M]^+$; found: 523.2070.

(2*S*,3*R*,4*S*,4a*R*,11b*R*)-7-methoxy-6-oxo-1,2,3,4,4a,5,6,11b-octahydro-[1,3]dioxolo [4,5-*j*]phenanthridine-2,3,4-triyl triacetate (22):

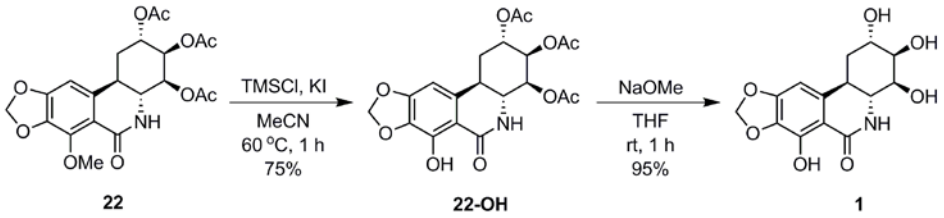


To a stirred solution of triacetate **21** (100 mg, 0.19 mmol, 1.0 equiv) in CH_2Cl_2 (9 mL) was added 2-chloropyridine (1.0 m soln. in CH_2Cl_2, 0.3 mL, 0.29 mmol, 1.5 equiv) and triflic anhydride (0.2 m soln. in CH_2Cl_2, 1.1. mL, 0.21 mmol, 1.1 equiv) at −78 °C. After stirring at −78 °C for 30 min, the reaction mixture was warmed to 35 °C and stirred for an additional 20 h. After that, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution at 0 °C. This was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/Acetone, 1:1) to give the major isomer **22** (65 mg, 76%) as a white solid along with the minor isomer **23** (5 mg, 6%). $[\alpha]^{25}_D$ +131.3 (*c* = 0.15, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.64 (br s, 1H), 1.85 (dt, *J* = 2.8, 13.6 Hz, 1H), 2.05 (s, 6H), 2.12 (s, 3H), 2.38 (d, *J* = 14.4 Hz, 1H), 3.05 (dt, *J* = 3.8, 12.4 Hz, 1H), 3.64 (t, *J* = 11.6 Hz, 1H), 4.04 (s, 3H), 5.13 (d, *J* = 3.0 Hz, 1H), 5,16 (d, *J* = 3.0 Hz, 1H), 5.40 (t, *J* = 3.0 Hz, 1H), 5.98 (d, *J* = 7.8 Hz, 2H), 6.14 (br s, 1H), 6.44 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.68, 20.76, 21.02, 26.95, 35.94, 52.12, 60.81, 67.37, 68.57, 71.49, 98.98, 101.68, 115.51, 137.13, 137.41, 145.08, 152.06, 163.75, 169.13, 169.38, 170.37 ppm; IR ($CHCl_3$): υ_{max} = 3197, 2926, 1752, 1669, 1612 cm^{-1}; MS (FAB): *m/z*: 450 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{21}H_{24}NO_{10}$: 450.1400 $[M+H]^+$; found: 450.1409.

Characterization of isocyanate 35

During the above reaction sequence (in this case, 1.5 equiv of Tf_2O and 3.0 equiv of 2-ClPy were used), isocyanate **35** could be obtained by quenching the reaction mixture with aqueous $NaHCO_3$ solution, before raising the temperature. This was then diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by short flash chromatography on silica gel (hexane/EtOAc, 1:1) to give isocyanate **35**. Since the compound appeared to decompose during the chromatography, the yield was not checked. The identity of isocyanate was confirmed by IR spectroscopy (2253 cm^{-1}). IR ($CHCl_3$): υ_{max} = 3014, 2939, 2852, **2253**, 1752, 1634, 1514 cm^{-1}.

(+)-*trans*-dihydronarciclasine (1):



22 **22-OH** **1**

To a stirred solution of lactam **22** (50.0 mg, 0.11 mmol, 1.0 equiv) in MeCN (5 mL) was added KI (18.4 mg, 0.11 mmol, 1.0 equiv) and TMSCl (0.5 m soln. in MeCN, 0.3 mL, 0.14 mmol, 1.3 equiv). The reaction mixture was stirred for 1 h at 60 °C and quenched by the addition of H_2O at 0 °C. This was diluted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 1:1) to give **22-OH** (36.2 mg, 75%) as a

white solid. $[\alpha]^{25}_{D}$ +81.8 (*c* = 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90 (dt, *J* = 2.7, 13.5 Hz, 1H), 2.07 (s, 6H), 2.12 (s, 3H), 2.41 (d, *J* = 14.5 Hz, 1H), 3.12 (dt, *J* = 3.6, 12.6 Hz, 1H), 3.76 (dd, *J* = 11.0, 12.7 Hz, 1H), 5.14−5.20 (m, 2H), 5.42 (t, *J* = 3.0 Hz, 1H), 5.98 (br s, 1H), 6.02 (d, *J* = 4.1 Hz, 2H), 6.31 (s, 1H), 12.29 ppm (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.70, 20.78, 21.03, 26.67, 34.55, 52.75, 67.23, 68.43, 71.62, 96.71, 102.33, 106.94, 133.18, 135.78, 146.47, 152.95, 169.15, 169.33, 170.13 ppm (2C); IR ($CHCl_3$): υ_{max} = 3335, 2924, 1752, 1673, 1627 cm^{-1}; MS (FAB): *m/z*: 436 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{20}H_{22}NO_{10}$: 436.1244 $[M+H]^+$; found: 436.1245.

To a solution of **22-OH** (30.0 mg, 0.07 mmol, 1.0 equiv) in THF (7 mL) was added NaOMe (1.0 m soln. in MeOH, 0.7 mL, 10.0 equiv). After being stirred at room temperature for 1 h, the reaction was quenched by the addition of saturated NH_4Cl solution, and extracted three times with EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (EtOAc/MeOH, 10:1) to give (+)-*trans*-dihydronarciclasine **1** (20.3 mg, 95%) as a white solid. $[\alpha]^{25}_{D}$ +4.0 (*c* = 0.16, THF), (Literature.[4b] $[\alpha]^{25}_{D}$ +4.1 (*c* = 0.22, THF)); ^{1}H NMR (400 MHz, CD_3OD): δ = 1.78−1.87 (m, 1H), 2.17−2.25 (m, 1H), 2.99 (dt, *J* = 3.4, 12.6 Hz, 1H), 3.46 (dd, *J* = 10.1, 13.0 Hz, 1H), 3.85 (dd, *J* = 3.0, 10.1 Hz, 1H), 3.90 (t, *J* = 2.9 Hz, 1H), 4.04−4.09 (m, 1H), 5.99 (d, *J* = 2.4 Hz, 2H), 6.44 ppm (s, 1H); ^{13}C NMR (125 MHz, CD_3OD): δ = 30.43, 36.06, 57.17, 71.35, 72.33, 74.14, 98.47, 104.22, 109.05, 134.72, 140.53, 148.06, 155.10, 172.70 ppm; IR (neat): υ_{max} =

3354, 2923, 1625 cm^{-1}; MS (FAB): *m/z*: 310 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{14}H_{16}NO_7$: 310.0927 $[M+H]^+$; found: 310.0928.

IV-2.2. All the compounds of the Model studies and optimization process

IV-2.2.1. Representative procedure for preparation of *N*-Boc carbamate

***tert*-Butyl (2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (25)**:

NEt_3 (2.9 mL, 20.5 mmol, 2.0 equiv), DMAP (125 mg, 1.03 mmol, 0.1 equiv), and $(Boc)_2O$ (2.5 g, 11.3 mmol, 1.1 equiv) were added to a solution of 2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethanamine[34] (2.0 g, 10.3 mmol, 1.0 equiv) in CH_2Cl_2 (52 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by the addition of brine at 0 °C. The mixture was then extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give *N*-Boc carbamate **25** (2.8 g, 93%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 9H), 2.66 (t, J = 6.9 Hz, 2H), 3.23−3.33 (m, 2H), 3.85 (s, 3H), 4.57 (br s, 1H), 5.89 (s, 2H), 6.31 (s, 1H), 6.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.36 (3C), 36.22, 41.87, 56.48, 79.22, 101.26, 102.75, 107.83, 133.44, 133.67, 143.52, 148.86, 155.80; IR ($CHCl_3$): υ_{max} = 3404, 3360, 2974, 2936, 1709, 1510 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{15}H_{22}NO_5$: 296.3389 $[M+H]^+$; found: 296.3396.

The amines required for the preparation of carbamate compounds **33a**-**33g**, **33i**, **33l**, and **33m** are commercially available. Carbamate **33h** were prepared from **33g** by simple *N*-methylation. The amines required for **33j** and **33k** were prepared by a previously developed procedure.[35]

***tert*-Butyl 3,4,5-trimethoxyphenethylcarbamate** (**33a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.72 (t, *J* = 6.9 Hz, 2H), 3.30−3.39 (m, 2H), 3.81 (s, 3H), 3.83 (s, 6H), 4.54 (br s, 1H), 6.38 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.37 (3C), 36.54, 41.72, 56.03 (2C), 60.78, 79.21, 105.62 (2C), 134.62, 136.50, 153.21 (2C), 155.82; IR ($CHCl_3$): υ_{max} = 3371, 2974, 2937, 1711 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{16}H_{26}NO_5$: 312.1811 [*M*+H]$^+$; found: 312.1820.

***tert*-Butyl 3,4-dimethoxyphenethylcarbamate** (**33b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 2.71 (t, *J* = 7.1 Hz, 2H), 3.28−3.35 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.51 (br s, 1H), 6.65−6.80 (m, 3H); HRMS (FAB): *m/z* calcd for $C_{15}H_{24}NO_4$: 282.1705 [*M*+H]$^+$; found: 282.1709.

***tert*-Butyl (2-(benzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate** (**33c**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.69 (t, *J* = 7.0 Hz, 2H), 3.27−3.35 (m, 2H), 4.51 (br s, 1H), 5.91 (s, 2H), 6.60−6.66 (m, 2H), 6.72 (d, *J* = 7.9 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{14}H_{20}NO_4$: 266.1392 [*M*+H]$^+$; found: 266.1395.

***tert*-Butyl 3-methoxyphenethylcarbamate** (**33d**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.75 (t, J = 7.0 Hz, 2H), 3.33−3.37 (m, 2H), 3.78 (s, 3H), 4.52 (br s, 1H), 6.72−6.77 (m, 3H), 7.20 (t, J = 7.8 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{14}H_{22}NO_3$: 252.1600 [M+H]$^+$; found: 252.1603.

***tert*-Butyl phenethylcarbamate** (**33e**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 2.83 (t, J = 7.3 Hz, 2H), 3.35−3.45 (m, 2H), 4.57 (br s, 1H), 7.16−7.38 (m, 5H); HRMS (FAB): *m/z* calcd for $C_{13}H_{20}NO_2$: 222.1494 [M+H]$^+$; found: 222.1490.

***tert*-Butyl 4-chlorophenethylcarbamate** (**33f**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H), 2.74 (t, J = 6.9 Hz, 2H), 3.23−3.36 (m, 2H), 4.50 (br s, 1H), 7.07−7.13 (m, 2H), 7.23−7.27 (m, 2H); HRMS (FAB): *m/z* calcd for $C_{13}H_{19}ClNO_2$: 256.1104 [M+H]$^+$; found: 256.1109.

***tert*-Butyl (2-(1*H*-indol-3-yl)ethyl)carbamate** (**33g**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.94 (t, J = 6.8 Hz, 2H), 3.38−3.51 (m, 2H), 4.60 (br s, 1H), 6.98−7.13 (m, 1H), 7.10 (dt, J = 1.0, 7.4 Hz, 1H), 7.19 (dt, J = 1.2, 7.6 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 8.07 (br s, 1H); HRMS (FAB): *m/z* calcd for $C_{15}H_{21}N_2O_2$: 261.1603 [M+H]$^+$; found: 261.1608.

***tert*-Butyl (2-(1-methyl-1*H*-indol-3-yl)ethyl)carbamate** (**33h**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.93 (t, *J* = 6.8 Hz, 2H), 3.42 (br s, 2H), 3.74 (s, 3H), 4.57 (br s, 1H), 6.87 (s, 1H), 7.07−7.11 (m, 1H), 7.19−7.30 (m, 2H), 7.57 (d, *J* = 7.7 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{16}H_{23}N_2O_2$: 275.1760 $[M+H]^+$; found: 275.1765.

***tert*-Butyl (2-(thiophen-3-yl)ethyl)carbamate** (**33i**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 2.80 (t, *J* = 6.9 Hz, 2H), 3.30−3.41 (m, 2H), 4.54 (br s, 1H), 6.92−6.98 (m, 2H), 7.25−7.27 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.35 (3C), 30.65, 40.99, 79.21, 121.25, 125.75, 128.05, 139.23, 155.80; IR ($CHCl_3$): υ_{max} = 3350, 2977, 2931, 1694 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{11}H_{18}NO_2S$: 228.1058 $[M+H]^+$; found: 228.1063.

***tert*-Butyl (3',5'-dimethoxy-[1,1'-biphenyl]-2-yl)carbamate** (**33j**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 3.80 (s, 6H), 6.48 (s, 3H), 6.60 (br s, 1H), 7.06 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.20 (dd, *J* = 1.7, 7.5 Hz, 1H) 7.32 (dt, *J* = 1.7, 8.4 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{19}H_{24}NO_4$: 330.1705 $[M+H]^+$; found: 330.1709.

***tert*-Butyl (3',4'-dimethoxy-[1,1'-biphenyl]-2-yl)carbamate** (**33k**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.45 (s, 9H), 3.88 (s, 3H), 3.93 (s, 3H), 6.54 (br s, 1H), 6.85−6.98 (m, 3H), 7.06 (dt, *J* = 1.2, 7.5 Hz, 1H), 7.20 (dd, *J* = 1.7, 7.5 Hz, 1H) 7.30 (dt, *J* = 1.4, 7.1 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.30 (3C), 55.88, 55.91,

80.40, 111.51, 112.30, 119.55, 121.46, 122.87, 128.15, 130.05, 130.70, 130.97, 135.34, 148.53, 149.09, 152.84; IR ($CHCl_3$): υ_{max} = 3345, 2977, 2934, 1730 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{19}H_{24}NO_4$: 330.1705 [*M*+H]$^+$; found: 330.1704.

***tert*-Butyl 3,4-dimethoxybenzylcarbamate** (**33l**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.48 (s, 9H), 3.84 (s, 6H), 4.21 (d, *J* = 5.3 Hz, 2H), 4.79 (br s, 1H), 6.74−6.83 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.31 (3C), 44.42, 55.72, 55.83, 79.27, 110.79, 111.09, 119.55, 131.56, 148.20, 148.99, 155.77; IR ($CHCl_3$): υ_{max} = 3352, 2975, 2934, 1725 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{14}H_{22}NO_4$: 268.1549 [*M*+H]$^+$; found: 268.1553.

***tert*-Butyl (3-(3,4-dimethoxyphenyl)propyl)carbamate** (**33m**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H), 1.77 (quintet, *J* = 7.4 Hz, 2H), 2.57 (t, *J* = 7.8 Hz, 2H), 3.05−3.20 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.50 (br s, 1H), 6.68−6.78 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 28.39 (3C), 31.92, 32.68, 40.19, 55.81, 55.92, 79.11, 111.31, 111.74, 120.13, 134.19, 147.27, 148.89, 155.95; IR ($CHCl_3$): υ_{max} = 3374, 2974, 2935, 1709 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{16}H_{26}NO_4$: 296.1862 [*M*+H]$^+$; found: 296.1862.

IV-2.2.2. Methyl (2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethyl)carbamate (**26**):

NEt_3 (2.9 mL, 20.5 mmol, 2.0 equiv), DMAP (125 mg, 1.03 mmol, 0.1 equiv), and methyl chloroformate (0.9 mL, 11.3 mmol, 1.1 equiv) were added to a solution of 2-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)ethanamine[34] (2.0 g, 10.3 mmol, 1.0 equiv) in CH_2Cl_2

(52 mL) at 0 °C. After stirring for 3 h at room temperature, the reaction was quenched by the addition of brine at 0 °C. The mixture was then extracted twice with CH_2Cl_2. The combined organic layers were washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexane/EtOAc, 2:1) to give methyl carbamate **26** (2.5 g, 95%) as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.69 (t, J = 6.8 Hz, 2H), 3.33−3.42 (m, 2H), 3.64 (s, 3H), 3.86 (s, 3H), 4.69 (br s, 1H), 5.91 (s, 2H), 6.31 (s, 1H), 6.34 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 36.18, 42.28, 52.03, 56.53, 101.29, 102.64, 107.90, 133.19, 133.75, 143.56, 148.93, 156.91; IR ($CHCl_3$): υ_{max} = 3340, 2942, 2890, 2843, 1697 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{12}H_{16}NO_5$: 254.1028 $[M+H]^+$; found: 254.1025.

IV-2.2.3. General procedure for the Friedel-Crafts-type cyclization associated with Table 1

The specified amount of base (DMAP, pyridine, or 2-chloropyridine) and triflic anhydride (1.0 M soln. in CH_2Cl_2) was added to a stirred solution of *N*-Boc carbamate **25** (89 mg, 0.30 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) at the specified temperature (0 ºC or -78 ºC). After 30 min, the reaction mixture was warmed to room temperature and stirred for the indicated duration. (In the case of entries 5, 6, and 7 of Table 1, Lewis acid was added after 20 min, stirred another 10 min and then warm to room temperature.) Then, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution at 0 ºC.

This solution was diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH, 20:1) to give the cyclized products **27** and **28** as a white solid. (When DMAP was replaced by the less basic pyridine or 2-chloropyridine (Table 1, entries 2 and 3), *N*-triflated derivatives **30** and **31** were also generated.) Isocyanate **32** could be obtained by quenching the reaction mixture with aqueous $NaHCO_3$ solution before the addition of Lewis acid.

4-Methoxy-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (**27**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.79 (t, J = 6.4 Hz, 2H), 3.37 (dt, J = 3.6, 6.3 Hz, 2H), 4.03 (s, 3H), 5.94 (s, 2H), 6.38 (s, 1H), 6.51 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.38, 39.69, 60.76, 101.37, 102.29, 115.68, 134.50, 137.04, 144.74, 151.26, 164.68; IR ($CHCl_3$): υ_{max} = 3406, 3221, 2929, 1664 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{11}H_{12}NO_4$: 222.0766 [M+H]$^+$; found: 222.0761.

4-Methoxy-7,8-dihydro-[1,3]dioxolo[4,5-*h*]isoquinolin-9(6*H*)-one (**28**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (t, J = 6.4 Hz, 2H), 3.47 (dt, J = 2.9, 6.4 Hz, 2H), 3.91 (s, 3H), 6.10 (s, 2H), 6.33 (s, 1H), 6.44 (br s, 1H); IR ($CHCl_3$): υ_{max} = 3179, 2991, 2903, 1657, 1636 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{11}H_{12}NO_4$: 222.0766 [M+H]$^+$; found: 222.0768.

4-Methoxy-6-((trifluoromethyl)sulfonyl)-7,8-dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (**30**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.97 (t, J = 6.0 Hz, 2H), 4.03 (t, J = 5.9 Hz, 2H), 4.05 (s, 3H), 6.01 (s, 2H), 6.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.22, 46.45, 60.64, 102.09, 102.29, 117.43, 121.72, 137.26, 137.51, 146.04, 153.72, 159.88; IR ($CHCl_3$): υ_{max} = 3008, 2956, 2905, 1700, 1608 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{12}H_{11}F_3NO_6S$: 354.0259 $[M+H]^+$; found: 354.0268.

4-Methoxy-8-((trifluoromethyl)sulfonyl)-7,8-dihydro-[1,3]dioxolo[4,5-*h*]isoquinolin-9(6*H*)-one (**31**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.05 (t, J = 5.9 Hz, 2H), 3.96 (s, 3H), 4.11 (t, J = 6.1 Hz, 2H), 6.14 (s, 2H), 6.36 (s, 1H); IR ($CHCl_3$): υ_{max} = 3010, 2981, 2911, 1678, 1603 (cm^{-1}); HRMS (FAB): *m/z* calcd for $C_{12}H_{11}F_3NO_6S$: 354.0259 $[M+H]^+$; found: 354.0265.

6-(2-Isocyanatoethyl)-4-methoxybenzo[*d*][1,3]dioxole (**32**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.79 (t, J = 6.8 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 3.88 (s, 3H), 5.96 (s, 2H), 6.36 (d, J = 1.5 Hz, 1H), 6.38 (d, J = 1.6 Hz,, 1H); IR ($CHCl_3$): υ_{max} = 2943, 2892, 2274, 1634, 1512 (cm^{-1}).

IV-2.2.4. Final optimized procedure for the Friedel-Crafts-type cyclization utilized in Table 2

Method A : 2-Chloropyridine (0.45 mmol, 1.5 equiv) and triflic anhydride (0.33 mmol, 1.1 equiv) were added to a stirred solution of *N*-Boc carbamate **33** (0.30 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) at -78 ºC. After 30 min, the reaction mixture was warmed to room temperature and stirred for 20 h. Next, the reaction mixture was quenched by the addition of saturated $NaHCO_3$ solution at 0 ºC, diluted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. This residue was purified by column chromatography on silica gel using an appropriate CH_2Cl_2/MeOH mixture as the eluent to yield the cyclized product **34**.

Method B : Identical to method A except for the addition of $BF_3 \cdot Et_2O$ 20 min after the addition of Tf_2O. In this case, the reaction was completed within 2 h.

6,7,8-Trimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**34a**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.86 (t, *J* = 6.3 Hz, 2H), 3.40−3.44 (m, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 3.93 (s, 3H), 6.01 (br s, 1H), 6.48 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{12}H_{16}NO_4$: 238.1079 $[M+H]^+$; found: 238.1083.

6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**34b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.91 (t, *J* = 6.8 Hz, 2H), 3.53 (dt, *J* = 2.8, 6.4 Hz, 2H), 3.91 (s, 6H), 6.01 (br s, 1H), 6.65 (s, 1H), 7.55 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{11}H_{14}NO_3$: 208.0974 $[M+H]^+$; found: 208.0979.

7,8-Dihydro-[1,3]dioxolo[4,5-*g*]isoquinolin-5(6*H*)-one (**34c**): ^{1}H NMR (300 MHz $CDCl_3$): δ = 2.86 (t, *J* = 6.6 Hz, 2H), 3.49 (t, *J* = 6.6 Hz, 2H), 5.97 (s, 2H), 6.62 (s, 1H), 6.80 (br s, 1H), 7.47 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{10}H_{10}NO_3$: 192.0661 $[M+H]^+$; found: 192.0657.

6-Methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (**34d**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.94 (t, *J* = 6.5 Hz, 2H), 3.52 (dt, *J* = 2.7, 6.5 Hz, 2H), 3.83 (s, 3H), 6.11 (br s, 1H), 6.68 (s, 1H), 6.83 (dd, *J* = 2.1, 8.6 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{10}H_{12}NO_2$: 178.0868 $[M+H]^+$; found: 178.0873.

2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (**34g**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.05 (t, *J* = 7.0 Hz, 2H), 3.71 (dt, *J* = 2.0, 6.9 Hz, 2H), 6.25 (br s, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 1H), 9.96 (br s, 1H); HRMS (FAB): *m/z* calcd for $C_{11}H_{11}N_2O$: 187.0871 $[M+H]^+$; found: 187.0876.

9-Methyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-one (**34h**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.04 (t, *J* = 6.9 Hz, 2H), 3.64 (dt, *J* = 2.7, 6.8 Hz, 2H), 4.10 (s, 3H), 5.57 (br s, 1H), 7.14 (dt, *J* = 1.1, 7.5 Hz, 1H), 7.32−7.38 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{12}H_{13}N_2O$: 201.1028 $[M+H]^+$; found: 201.1025.

5,6-Dihydrothieno[2,3-*c*]pyridin-7(4*H*)-one (**34i**): ^{1}H NMR (400 MHz, $CDCl_3$): δ =

2.90 (t, *J* = 6.9 Hz, 2H), 3.60 (dt, *J* = 2.2, 6.8 Hz, 2H), 6.48 (br s, 1H), 6.92 (d, *J* = 4.8 Hz, 1H), 7.47 (d, *J* = 4.8 Hz, 1H); HRMS (FAB): *m/z* calcd for C_7H_8NOS: 154.0327 $[M+H]^+$; found: 154.0328.

7,9-dimethoxyphenanthridin-6(5*H*)-one (**34j**): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.85 (s, 3H), 3.97 (s, 3H), 6.70 (d, *J* = 1.7 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.41−7.48 (m, 2H), 8.32 (d, *J* = 8.1 Hz, 1H); HRMS (FAB): *m/z* calcd for $C_{15}H_{14}NO_3$: 256.0974 $[M+H]^+$; found: 256.0979.

8,9-dimethoxyphenanthridin-6(5*H*)-one (**34k**): ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.90 (s, 3H), 4.02 (s, 3H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.43 (t, *J* = 7.6 Hz, 1H), 7.71 (s, 1H), 7.88 (s, 1H), 8.38 (d, *J* = 8.0 Hz, 1H), 11.56 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{15}H_{14}NO_3$: 256.0974 $[M+H]^+$; found: 256.0978.

7,8-Dimethoxy-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-one (**34m**): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.99 (quintet, *J* = 6.8 Hz, 2H), 2.80 (t, *J* = 7.1 Hz, 2H), 3.12 (q, *J* = 6.4 Hz, 2H), 3.89 (s, 3H), 3.90 (s, 3H), 6.22 (br s, 1H), 6.65 (s, 1H), 7.24 (s, 1H); HRMS (FAB): *m/z* calcd for $C_{12}H_{16}NO_3$: 222.1130 $[M+H]^+$; found: 222.1134.

IV-3. Analysis of molecular geometries of 15 and 16

***Theoretical Calculations*:** Theoretical calculations of regioisomers **15b (A)** and **16b (B)** were performed using the DMol^3 module in Material Studio 5.5^{TM}. The two regioisomers were optimized by the density functional theory (DFT) at the DNP level. A generalized gradient approximation (GAA) for the exchange correlation function of Perdew, Burke, and Ernzerhof (PBE) was used with the double-numerical plus polarization (DNP) as implemented in DMol^3.

The computational energy minimization using DMol^3 program suggests that product **15b** is thermodynamically more stable than other conformer **16b**, which is consistent with the experimental result. The calculated energy difference between **15b** and **16b** is about 1.3586 kcal/mol.

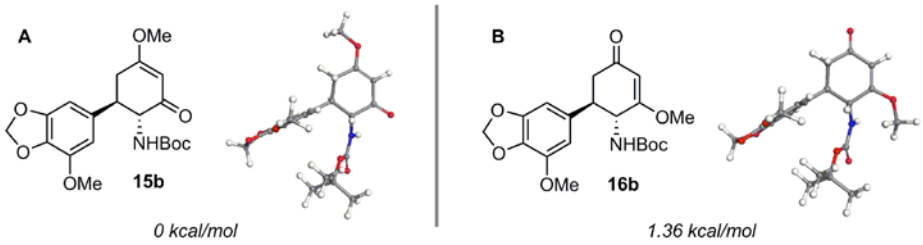


Figure 1. Density functional calculations at the PBE/DNP level on **15b** and **16b**.

Compound	*Hartree (Ha)*	*kcal/mol*	*Relative energy (kcal/mol)*
15b	-1.357390686 x 10^3	-851775.403 x 10^5	0
16b	-1.357388521 x 10^3	-851774.0444 x 10^5	1.358621

1Ha = 627.509391 kcal/mol

$\triangle G = -RTlnK$ (R = 0.001987 kcal K^{-1} mol^{-1}, T= 293.15 K)

lnK = (-1.358621 kcal/mol) / (-0.001987 kcal K^{-1} mol^{-1} x 293.15 K) = 2.3324

$K = e^{2.3324} = 10.303$

***Calculation input*:** All calculations are performed under following conditions.

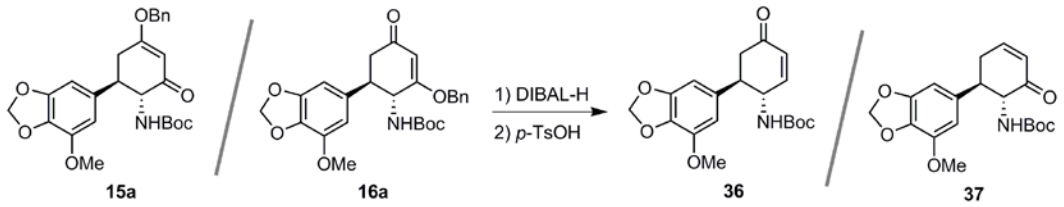
 # Task parameters

Calculate	optimize
Opt_energy_convergence	1.0000e–005
Opt_gradient_convergence	2.0000e–003 A
Opt_displacement_convergence	5.0000e–003 A
Opt_iterations	50
Opt_max_displacement	0.3000 A
Symmetry	0ff
Max_memory	4096

 # Electronic parameters

Spin_polarization	restricted
Charge	0
Basis	dnp
Pseudopotential	none
Functional	pbe
Aux_density	octupole
Integration_grid	fine
Occupation	fermi
Cutoff_Global	3.7000 angstrom
Scf_density_convergence	1.0000e–006
Scf_charge_mixing	0.2000
Scf_iterations	50
Scf_diis	6 pulay

***2D COSY NMR analysis of Enones*:** The chemical identities of **15a** and **16a** are also supported by the results of 2D COSY NMR experiments conducted on the corresponding enones **36** and **37**. Enones **36** and **37** were easily synthesized from vinylogous benzyl esters **15a** and **16a** by the well-known sequence (hydride reduction and acid hydrolysis) as shown below.[36]



***tert*-butyl (1*S*,6*R*)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-4-oxocyclohex-2-enylcarbamate (36):** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (s, 9H), 2.61−2.75 (m, 2H), 3.11−3.25 (m, 1H), 3.88 (s, 3H), 4.56 (br s, 2H), 5.94 (s, 2H), 6.06 (d, J = 9.9 Hz, 1H), 6.36−6.48 (m, 2H), 6.92 ppm (d, J = 9.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.18 (3C), 44.96, 48.13, 56.68, 60.37, 80.16, 101.35, 101.49, 107.22, 129.22, 134.48, 134.50, 141.61, 149.17, 152.23, 155.13, 197,54 ppm; MS (FAB): *m/z*: 362 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{24}NO_6$: 362.1604 $[M+H]^+$; found: 362.1609.

***tert*-butyl (1*R*,6*R*)-6-(7-methoxybenzo[*d*][1,3]dioxol-5-yl)-2-oxocyclohex-3-enylcarbamate (37):** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9H), 2.63−2.70 (m, 2H), 3.11−3.22 (m, 1H), 3.88 (s, 3H), 4.47−4.60 (m, 1H), 4.61−4.72 (m, 1H), 5.92 (dd, J = 1.2, 4.6 Hz, 2H), 6.14 (d, J = 10.2, Hz, 1H), 6.43−6.49 (m, 2H), 6.95 ppm (td, J = 3.7, 9.7 Hz,

1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.14 (3C), 35.74, 48.29, 56.58, 60.49, 79.66, 101.38, 101.90, 127.27, 128.76, 134.27, 134.88, 143.46, 148.40, 148.81, 155.76, 196.66 ppm; MS (FAB): *m/z*: 362 $[M+1]^+$; HRMS (FAB): *m/z* calcd for $C_{19}H_{24}NO_6$: 362.1604 $[M+H]^+$; found: 362.1607.

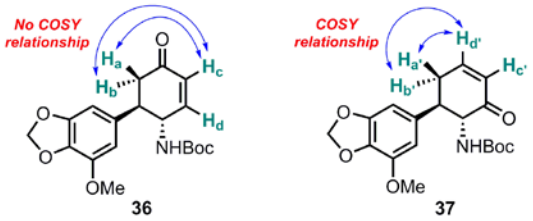


Figure 2. Rationale for using COSY relationships to distinguish between enones **36** and **37**.

V. References

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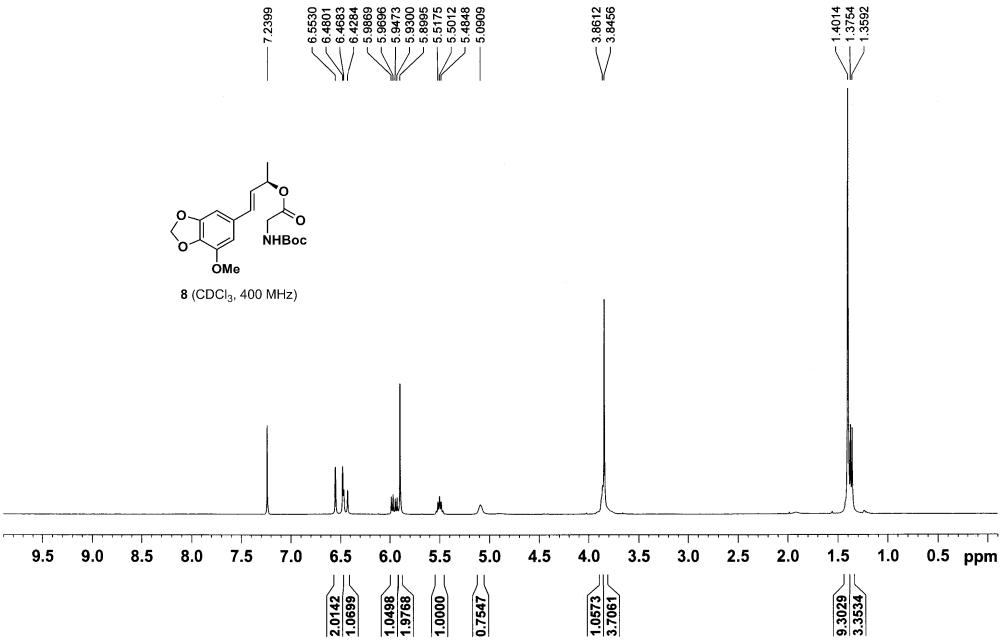
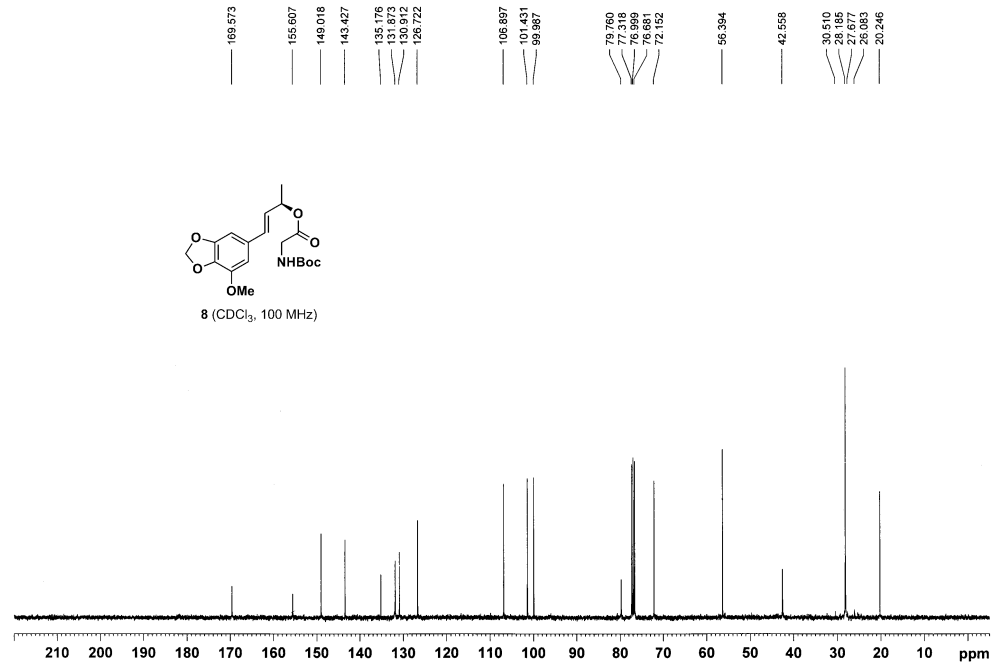
Appendix I.

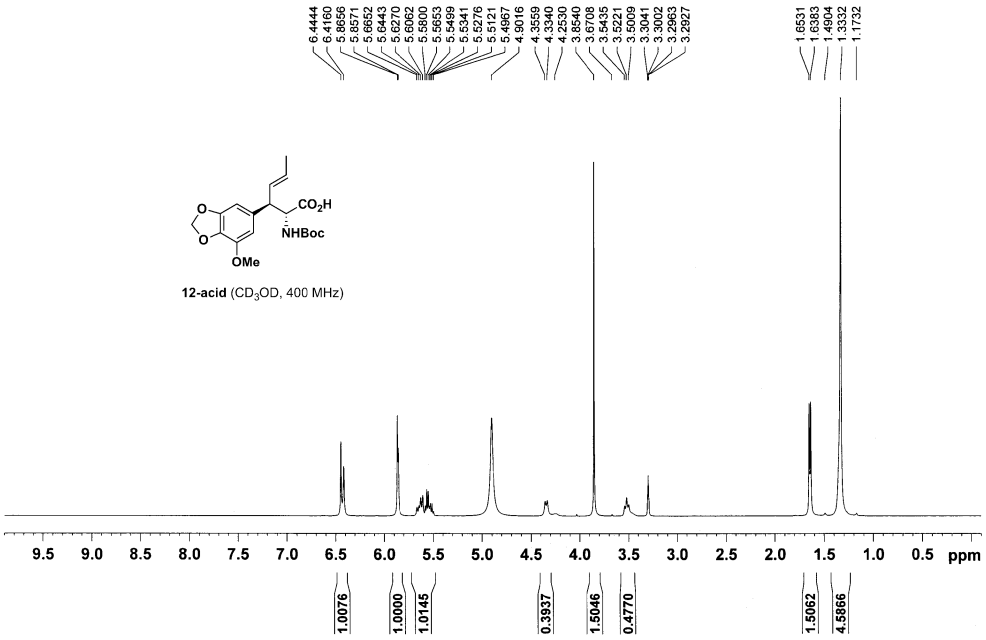
Spectra of Compounds.

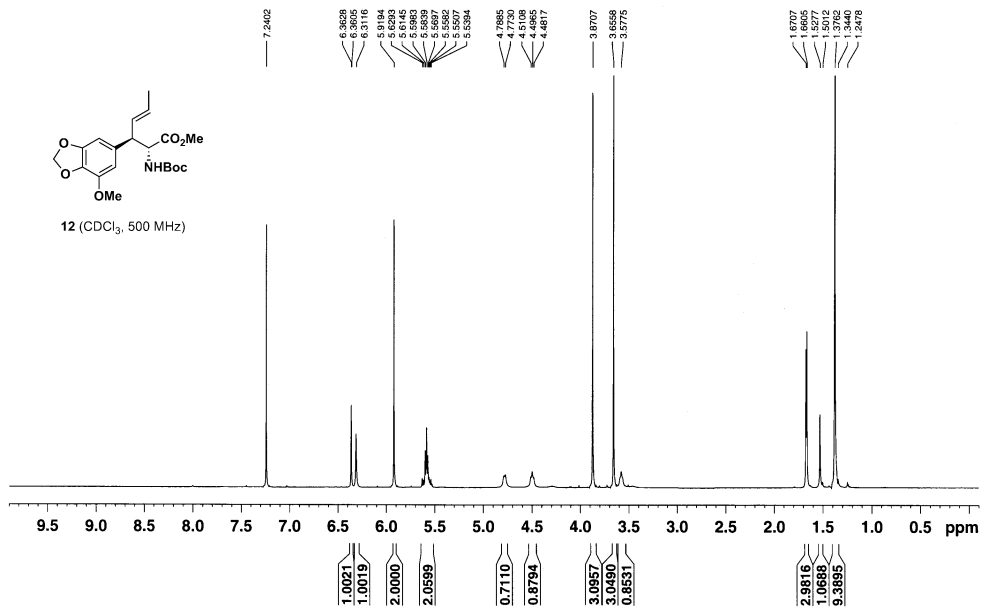
- ^{1}H & ^{13}C NMR spectrum of compound **8**



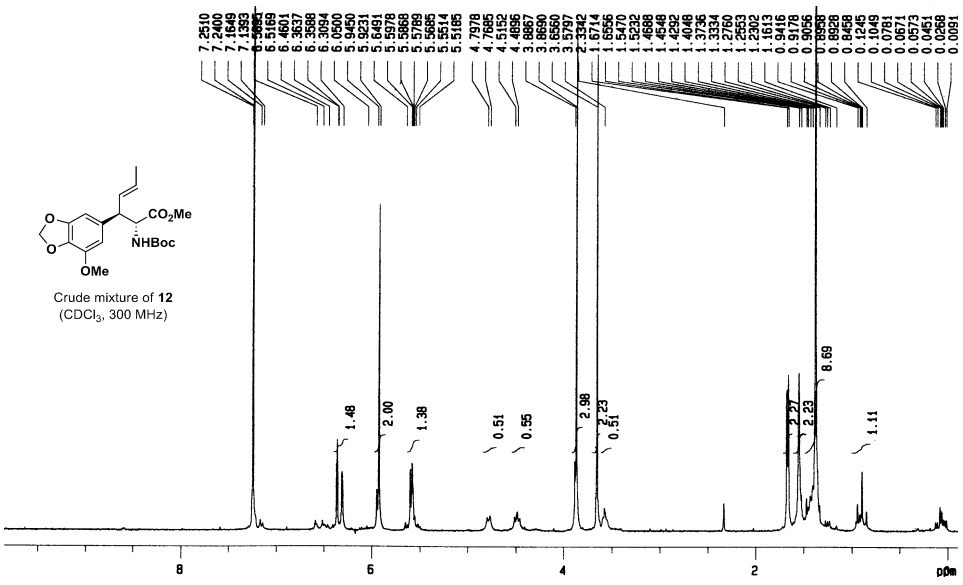


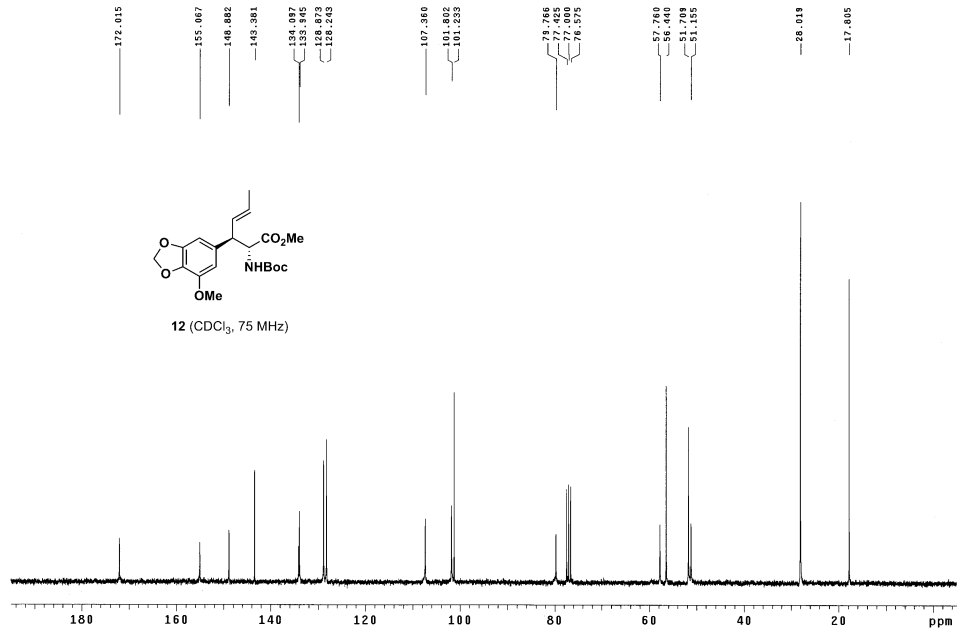
- ^{1}H NMR spectrum of compound **12-acid** & **12**





- Crude ^{1}H NMR spectrum of compound **12** & ^{13}C NMR spectrum of compound **12**



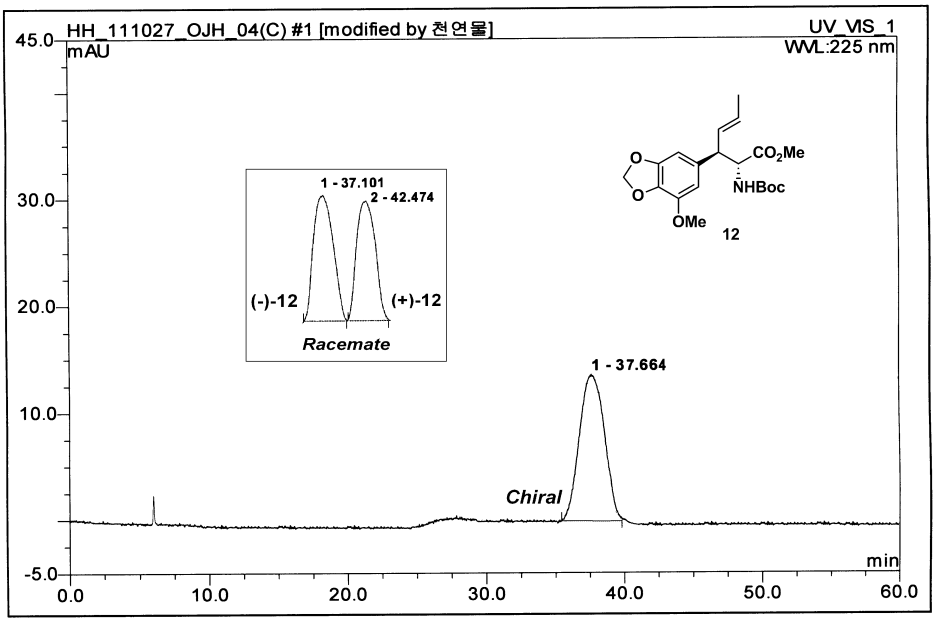


- Chiral HPLC spectrum of compound **12**

2011-10-28 4:48 PM

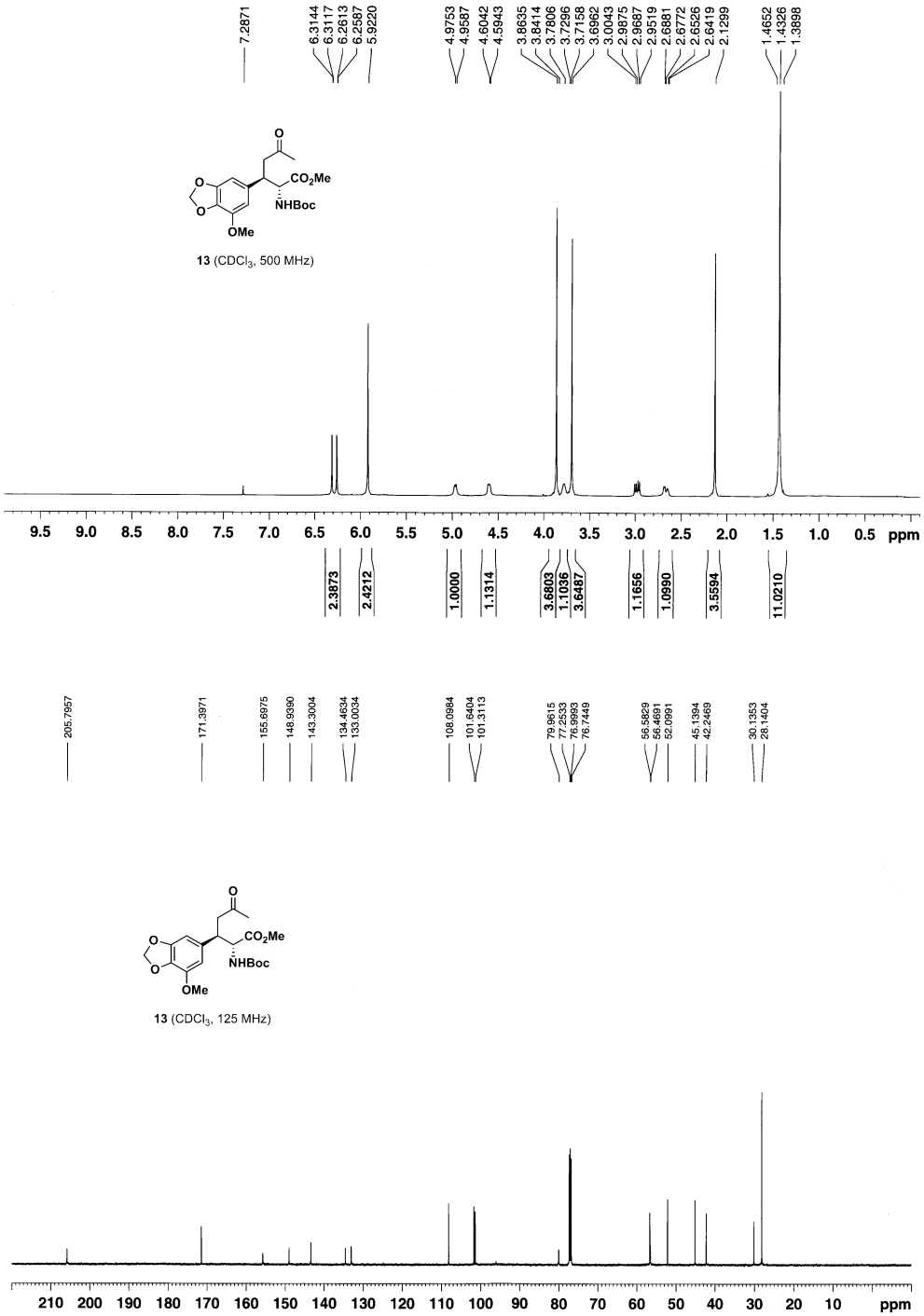
1 HH_111027_OJH_04

Sample Name:	**HH_111027_OJH_04**	*Injection Volume:*	**10.0**
Vial Number:	**RA2**	*Channel:*	**UV_VIS_1**
Sample Type:	**unknown**	*Wavelength:*	**225**
Control Program:	**HH_Gradient_0 to 10_05ml_60min**	*Bandwidth:*	**1**
Quantif. Method:	**HH_Gradient_0 to 10_05ml_60min**	*Dilution Factor:*	**1.0000**
Recording Time:	**2011-10-27 21:55**	*Sample Weight:*	**1.0000**
Run Time (min):	**60.00**	*Sample Amount:*	**1.0000**

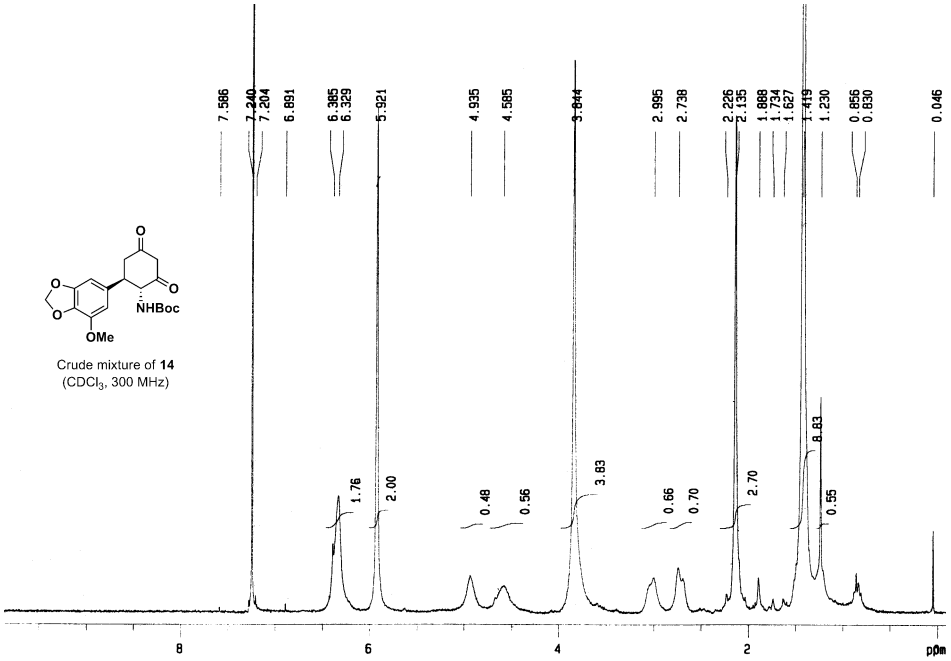


No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	37.66	n.a.	13.718	34.546	100.00	n.a.	BM *
Total:			13.718	34.546	100.00	0.000	

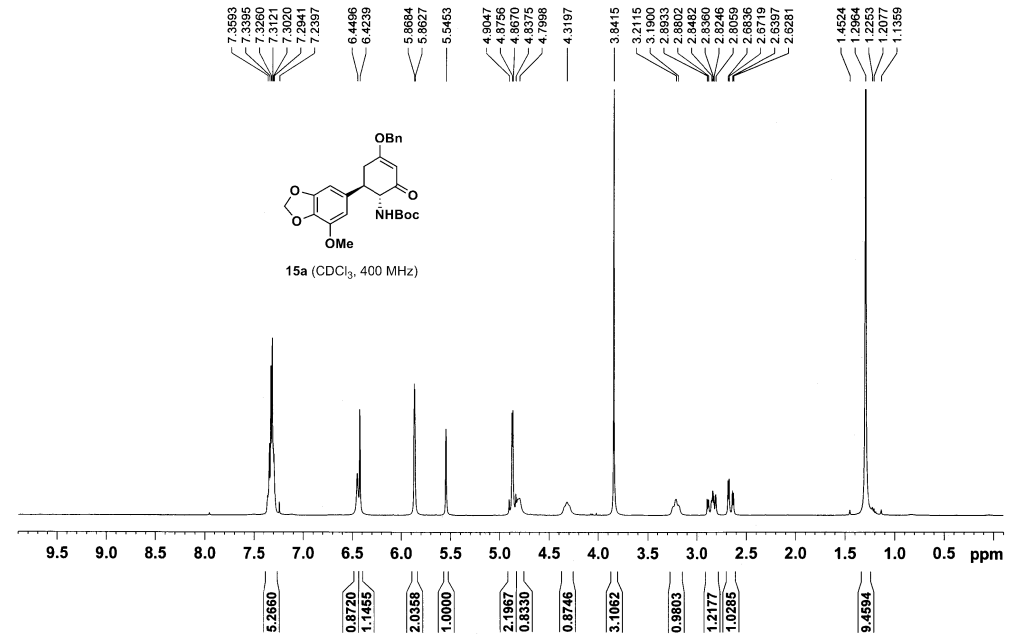
- ^{1}H & ^{13}C NMR spectrum of compound **13**

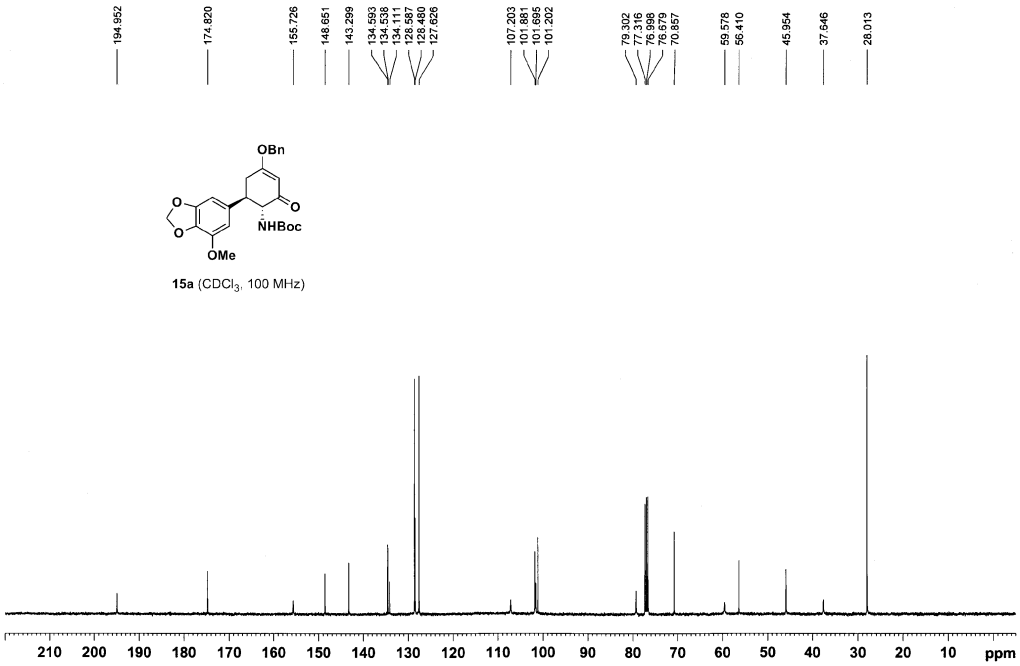


- Crude ^{1}H NMR spectrum of compound **14**

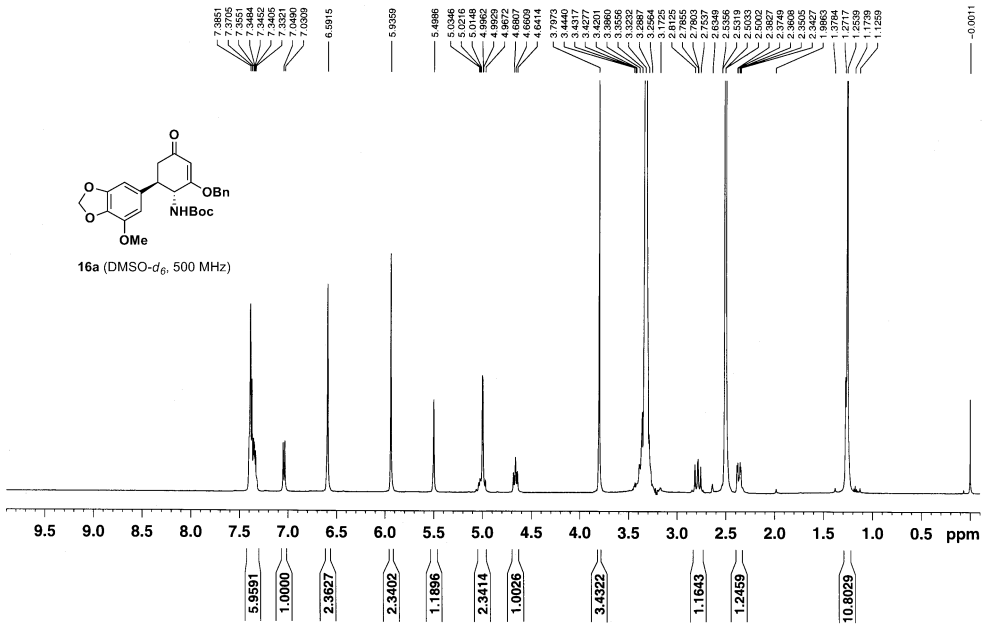


- ^{1}H & ^{13}C NMR spectrum of compound **15a**

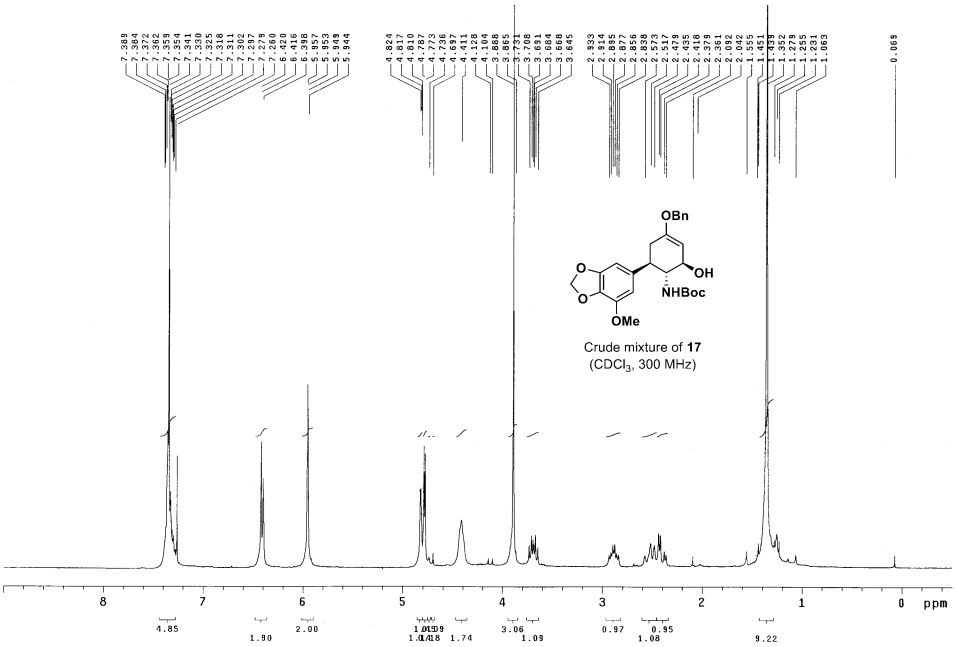


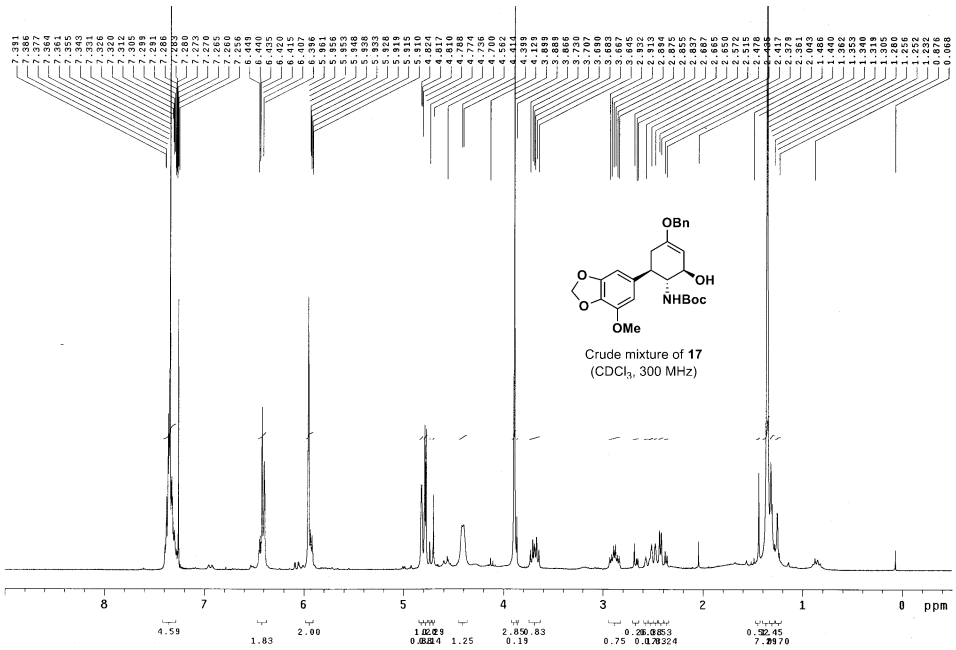


- ^{1}H NMR spectrum of compound **16a**

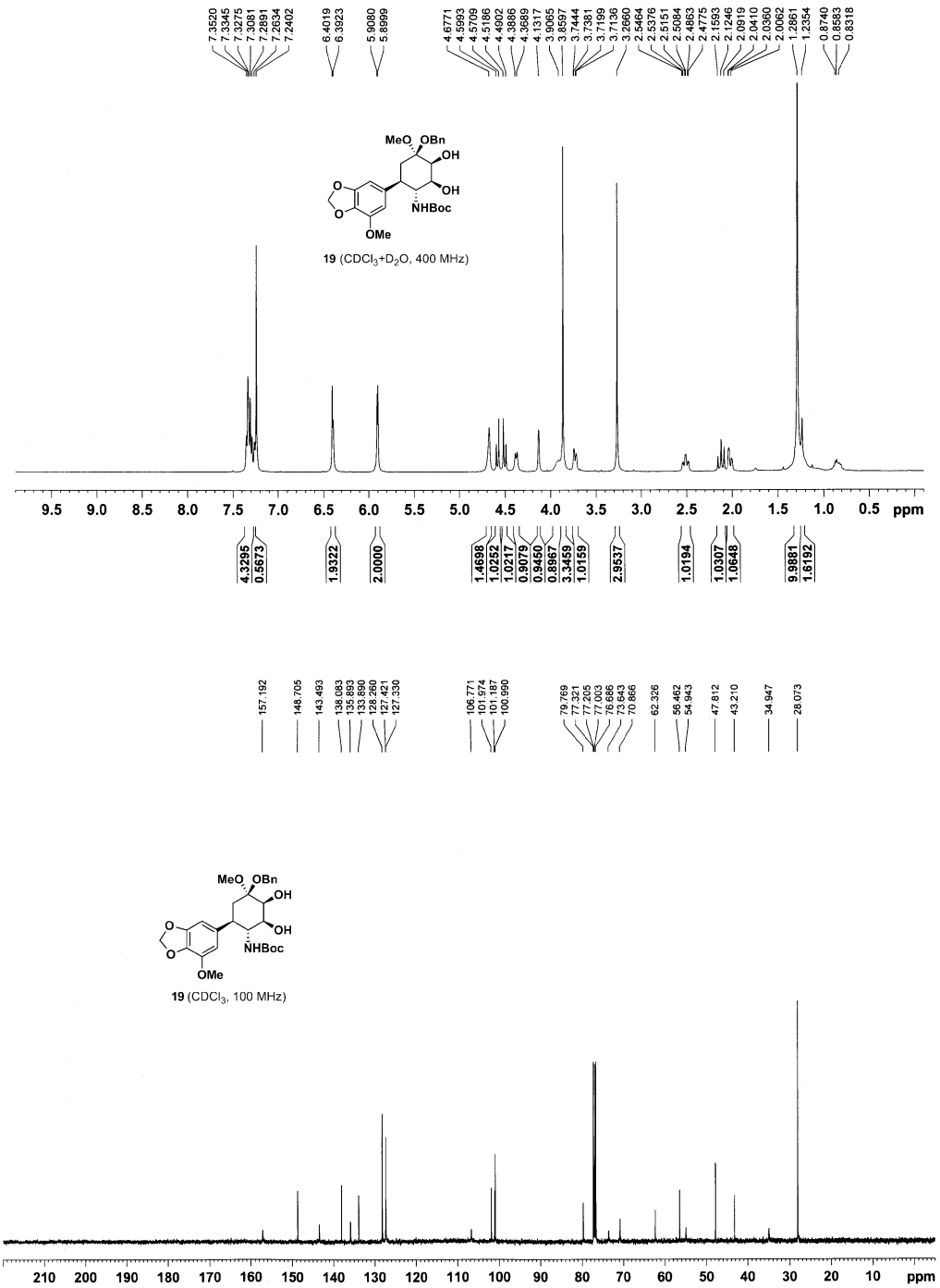


- Crude ^{1}H NMR spectrum of compound **17** (Red-Al (up) and LAH (down) reduction)

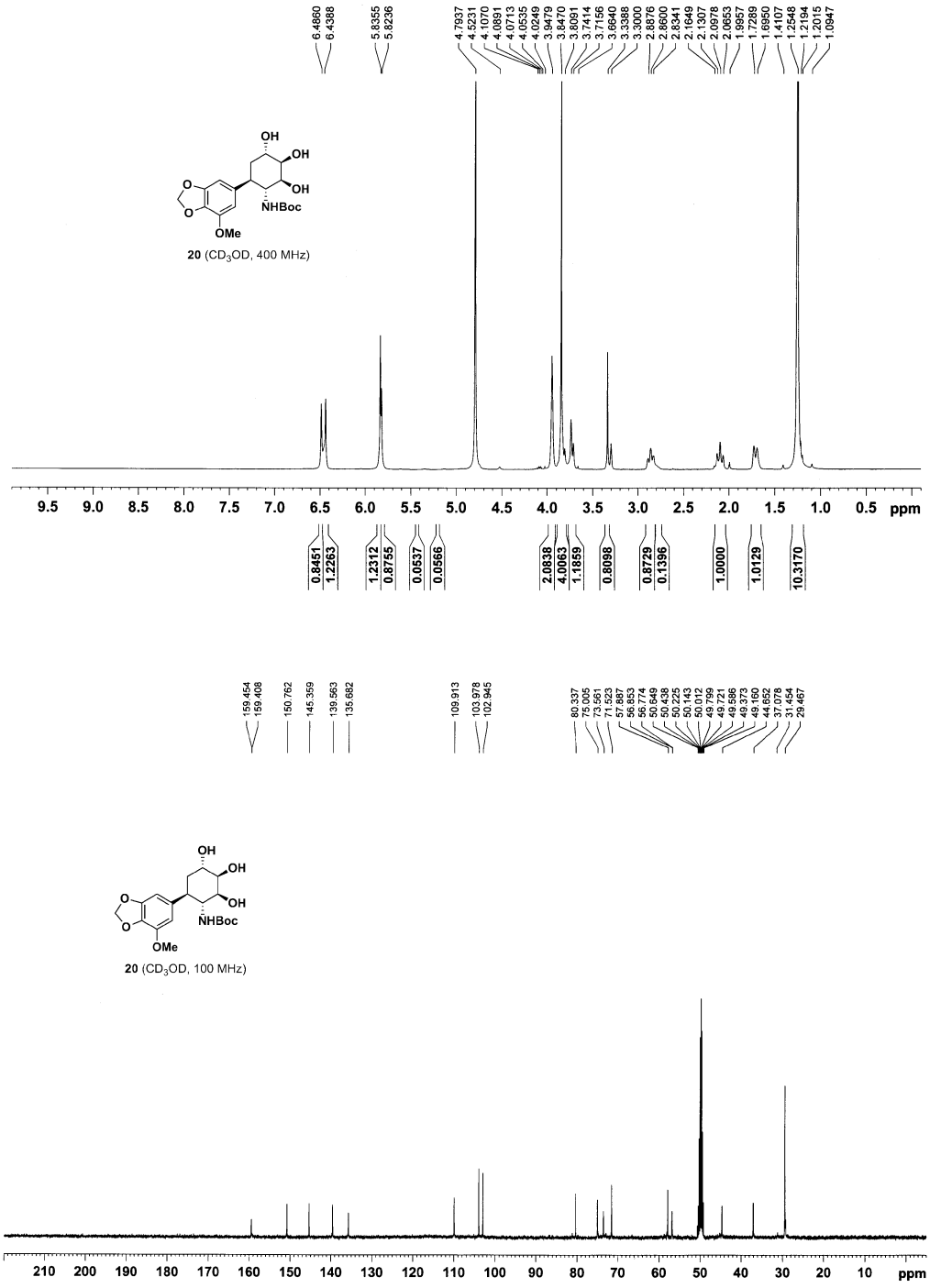




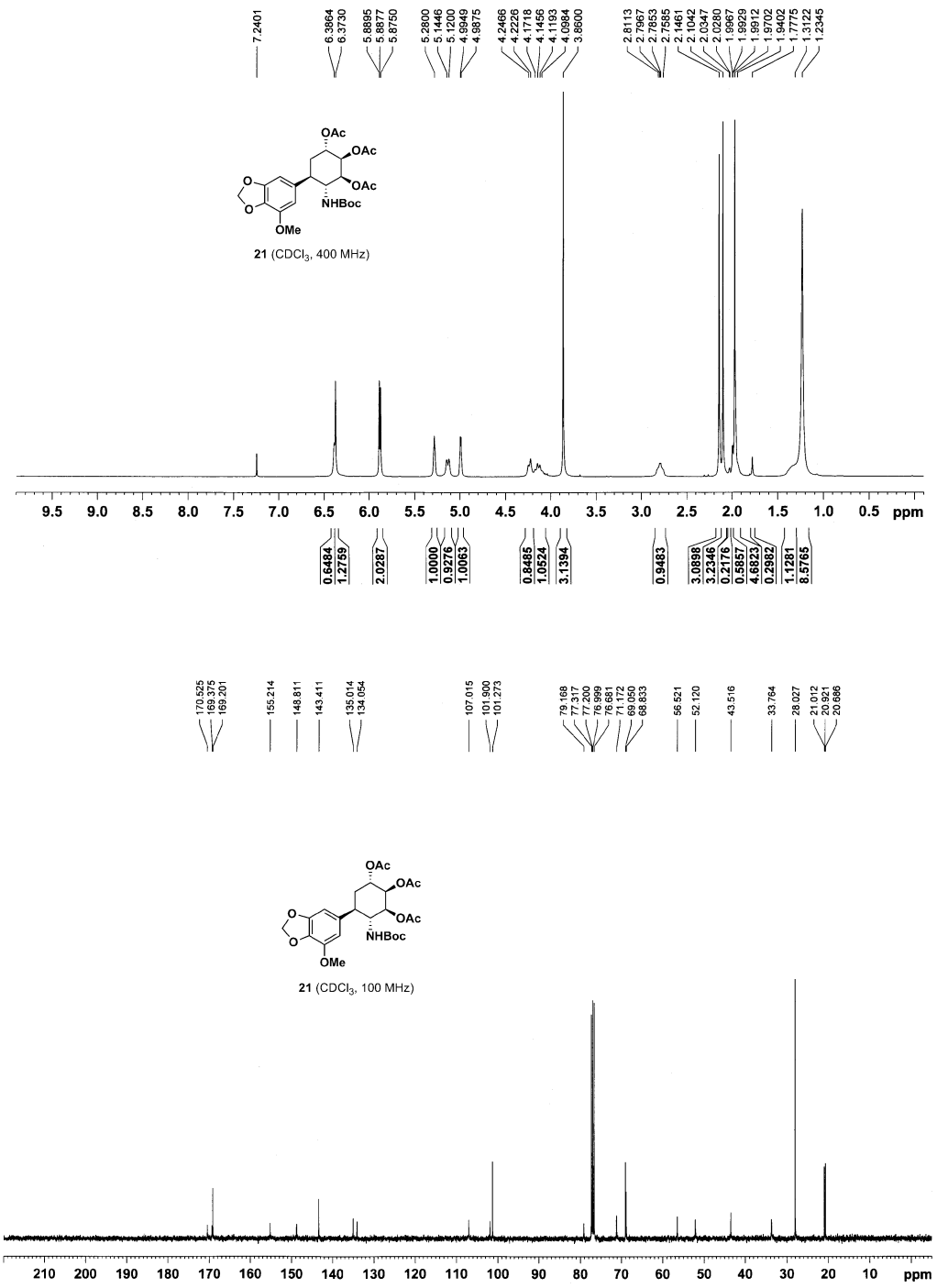
- ^{1}H & ^{13}C NMR spectrum of compound **19**



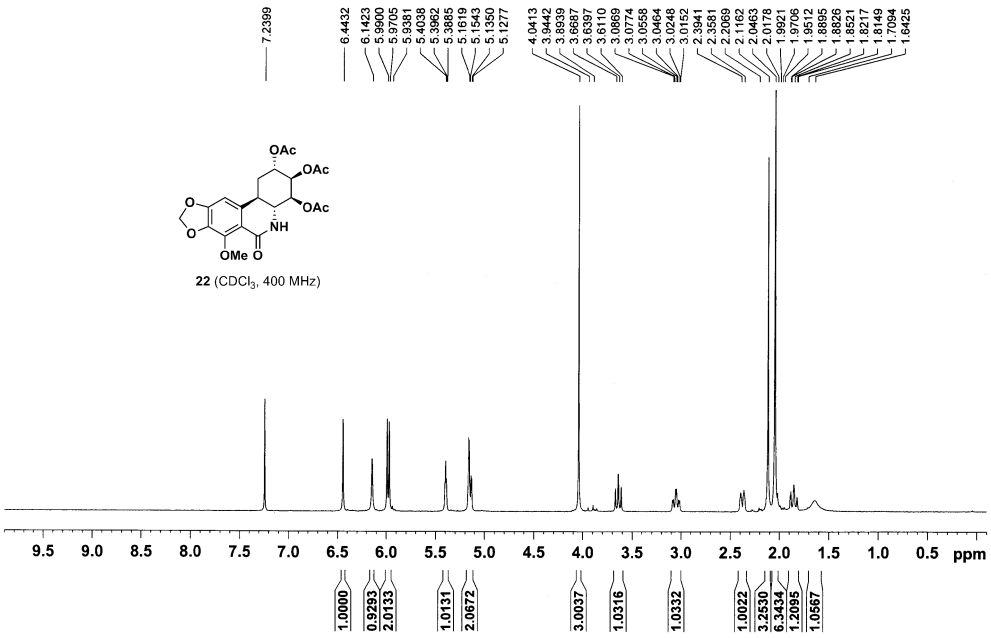
- ^{1}H & ^{13}C NMR spectrum of compound **20**

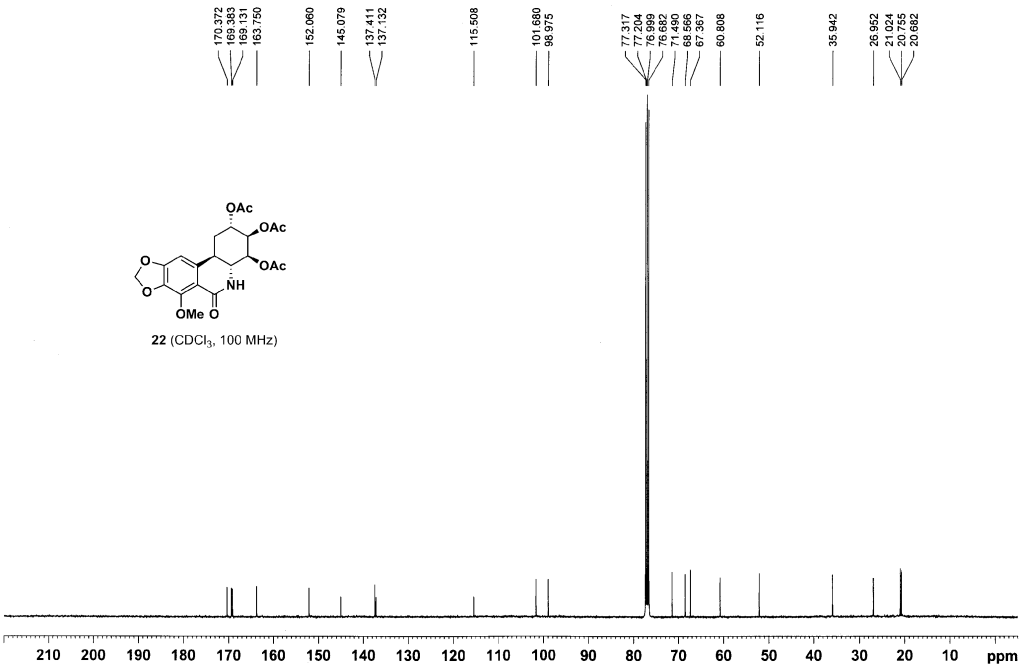


- ^{1}H & ^{13}C NMR spectrum of compound **21**

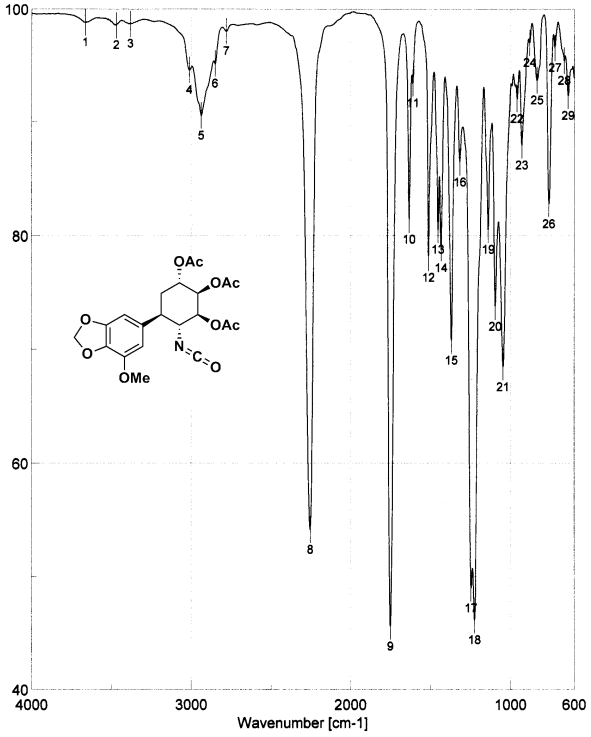


- ^{1}H & ^{13}C NMR spectrum of compound **22**





- IR spectrum of compound **35**



[Comment]
Sample Name HH2-VII-167
Comment
User
Division
Company SNU

[Data Information]
Creation Date 2012-03-21 오 2:53

Data array type Linear data array
Horizontal Wavenumber [cm-1]
Vertical %T
Start 599.753 cm-1
End 4000.6 cm-1
Data pitch 0.964233 cm-1
Data points 3528

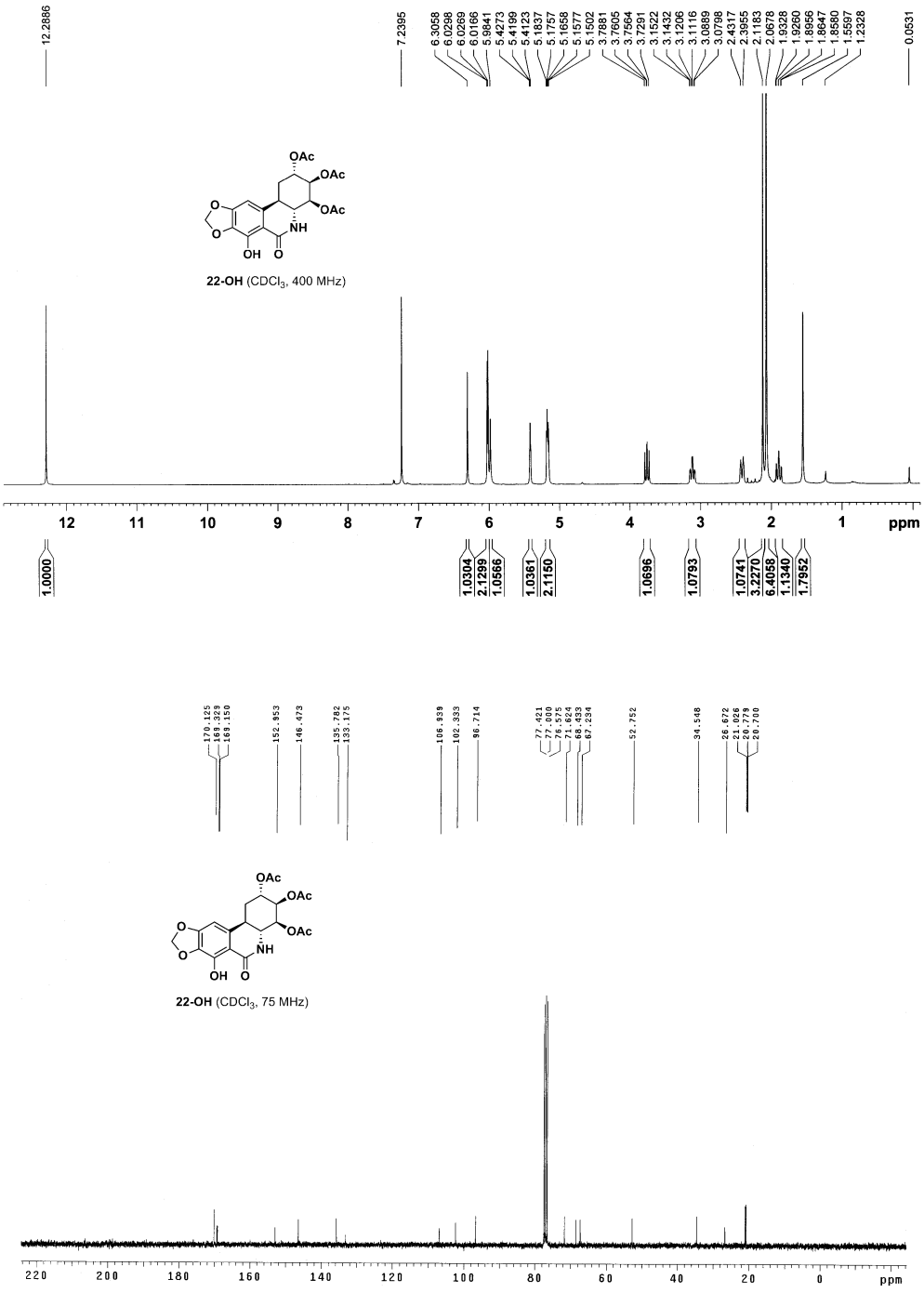
[Measurement Information]
Model Name FT/IR-4200typeA
Serial Number B038361018

Light Source Standard
Detector TGS
Accumulation Auto (18)
Resolution 4 cm-1
Zero Filling On
Apodization Cosine
Gain Auto (2)
Aperture Auto (7.1 mm)
Scanning Speed Auto (2 mm/sec)
Filter Auto (30000 Hz)

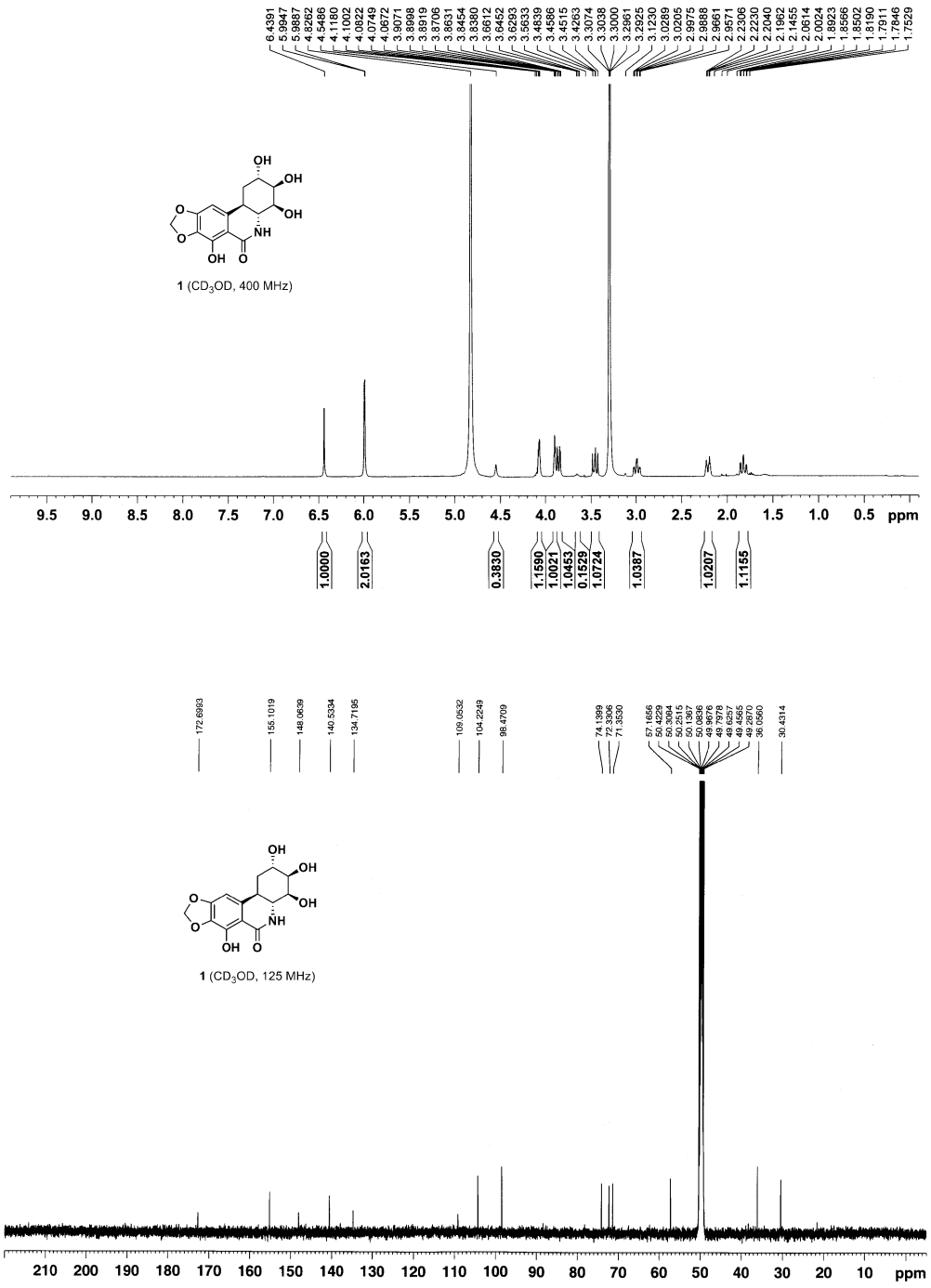
Result of Peak Picking

No.	Position	Intensity	No.	Position	Intensity
1	3664.09	98.7965	2	3471.24	98.5325
3	3382.53	98.666	4	3014.19	94.5563
5	2938.98	90.5326	6	2852.2	95.1199
7	2781.81	97.9918	8	2253.41	54.1165
9	1752.01	45.5667	10	1634.38	81.4038
11	1613.16	93.3776	12	1513.85	78.0448
13	1453.1	80.5185	14	1434.78	78.8909
15	1370.18	70.7728	16	1318.11	86.4369
17	1245.79	48.961	18	1224.58	46.1513
19	1138.76	80.5075	20	1094.4	73.7498
21	1046.19	68.444	22	959.412	91.9892
23	929.521	87.9136	24	881.309	96.9532
25	834.062	93.6268	26	757.888	82.7728
27	722.211	96.5186	28	664.357	95.3673
29	639.287	92.2801			

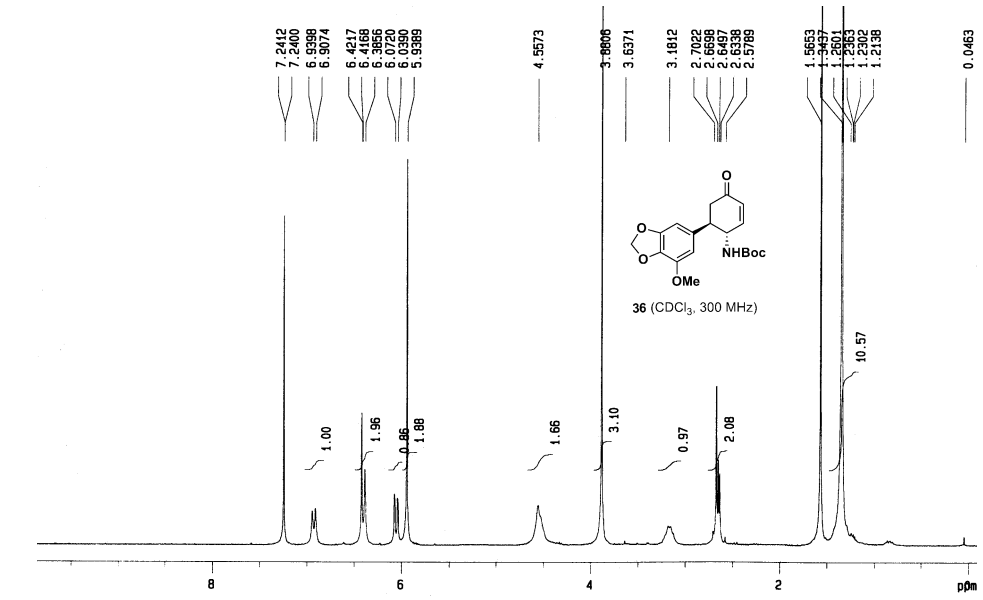
- ^{1}H & ^{13}C NMR spectrum of compound **22-OH**

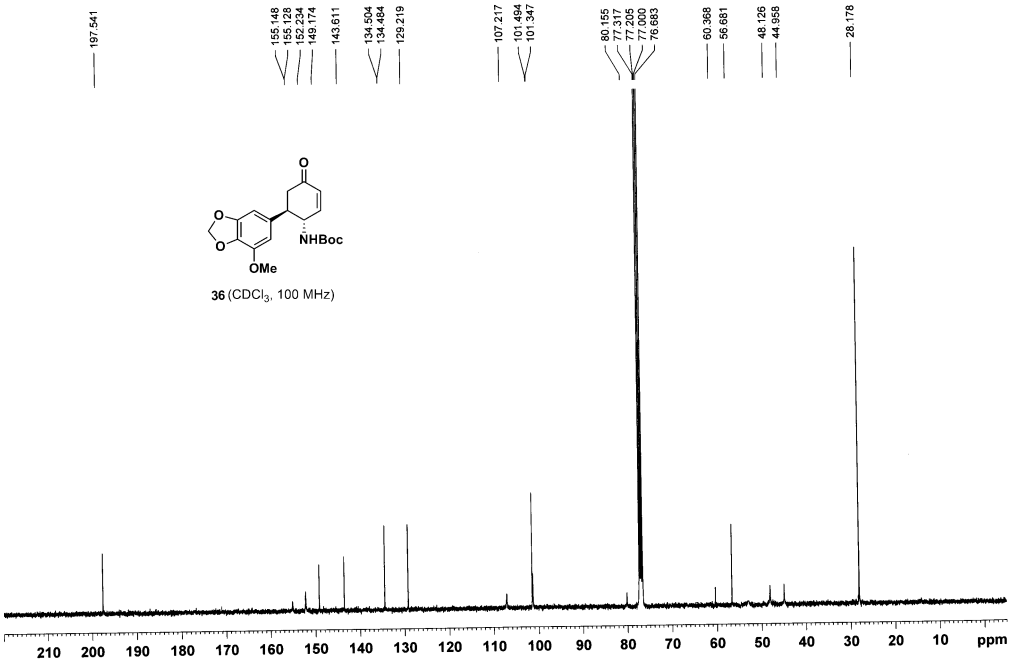


- ^{1}H & ^{13}C NMR spectrum of compound **1**

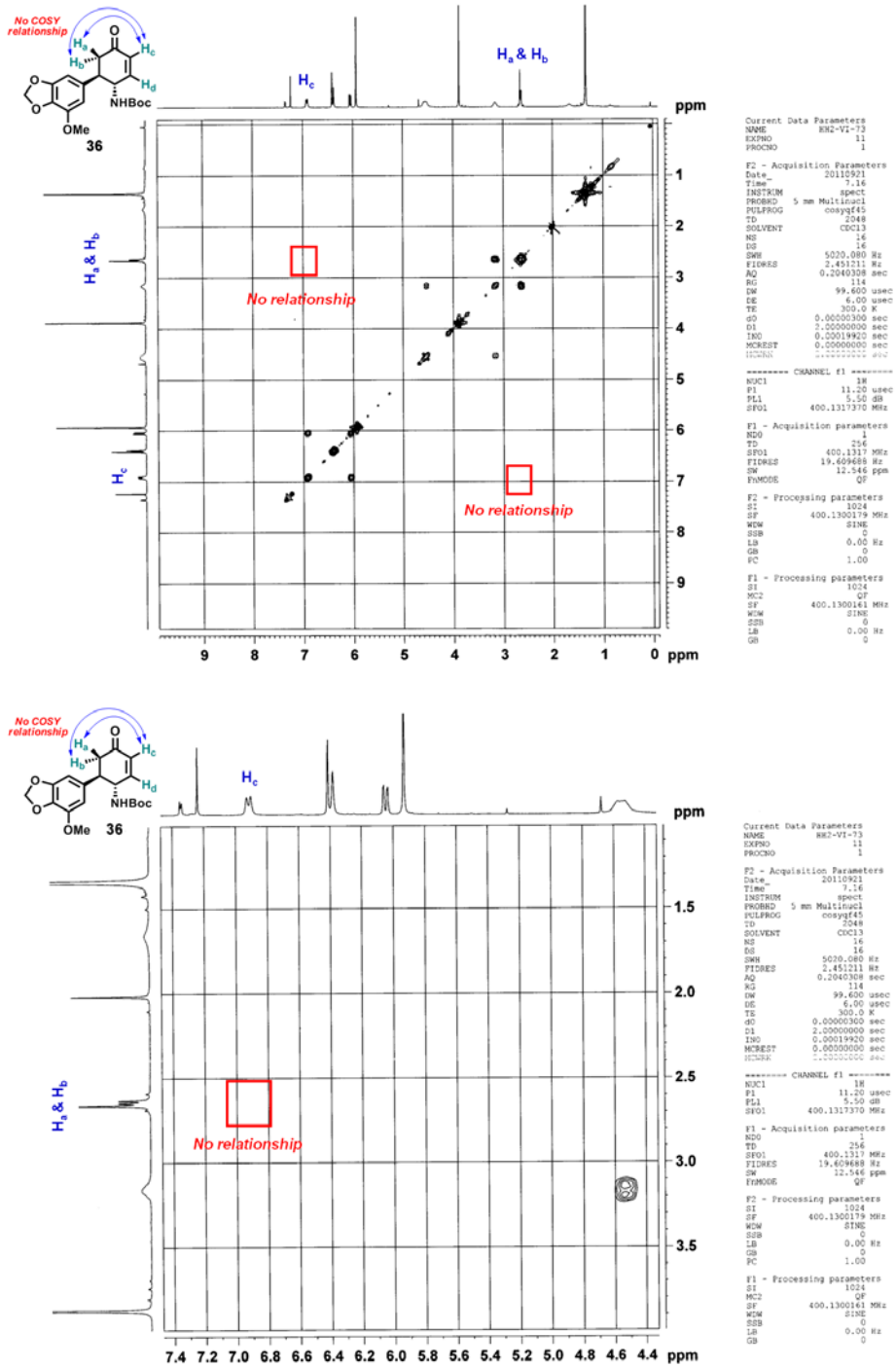


- ^{1}H & ^{13}C NMR spectrum of compound **36**

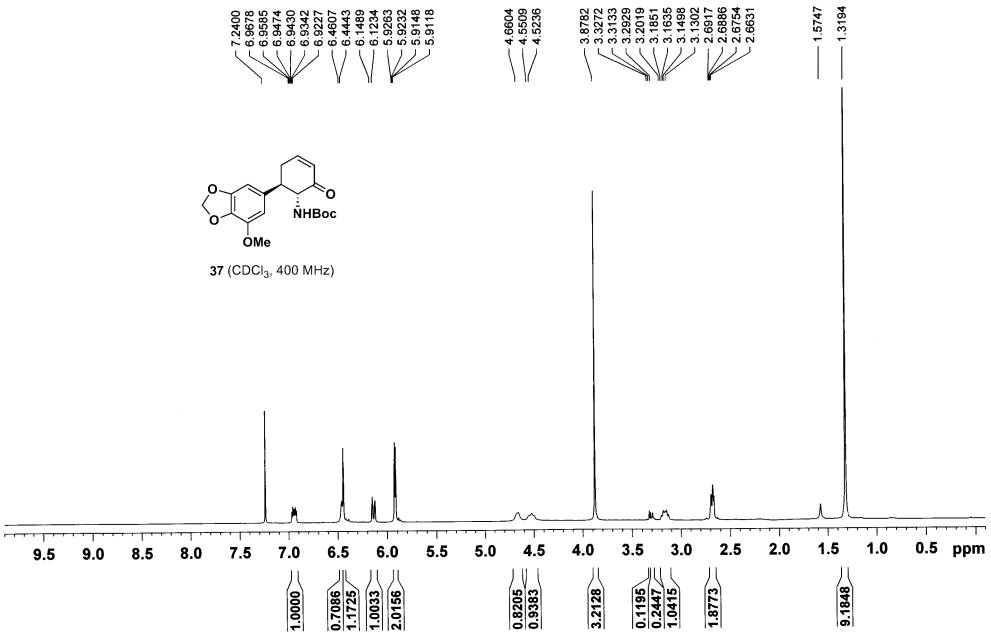


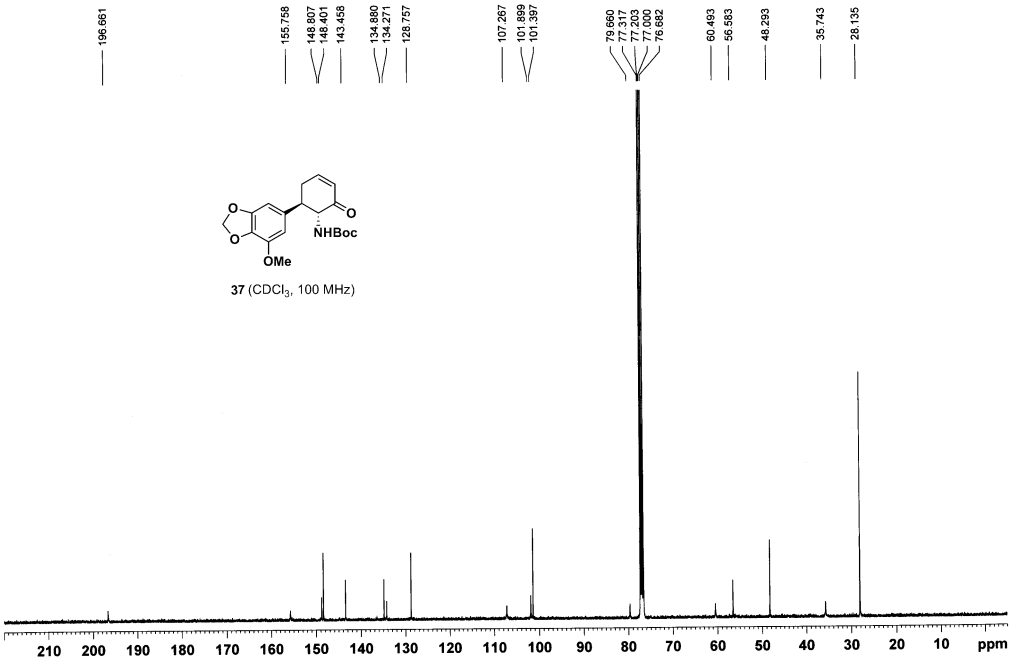


- ^{1}H-^{1}H COSY NMR spectrum of compound **36**

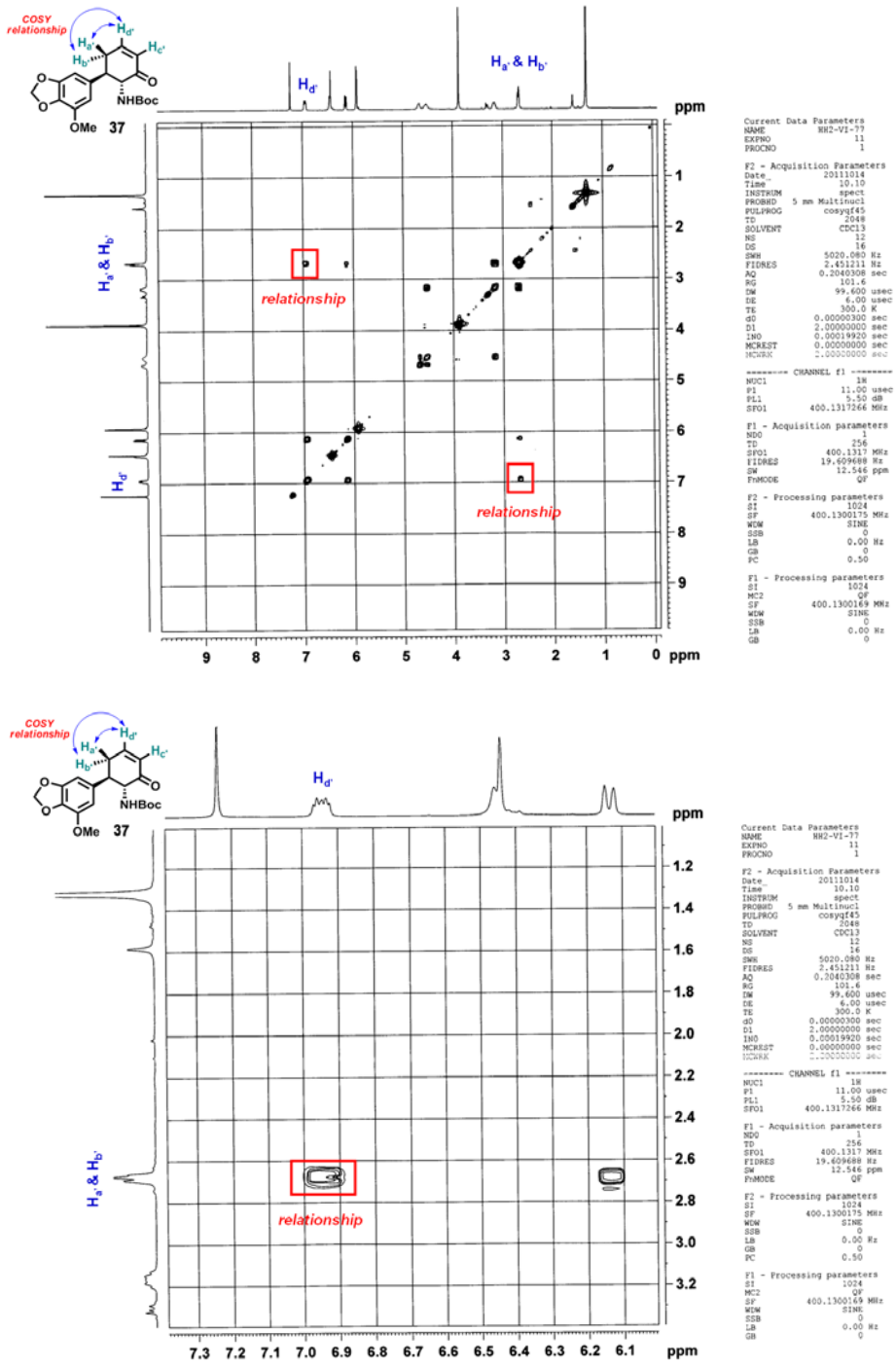


- ^{1}H & ^{13}C NMR spectrum of compound **37**

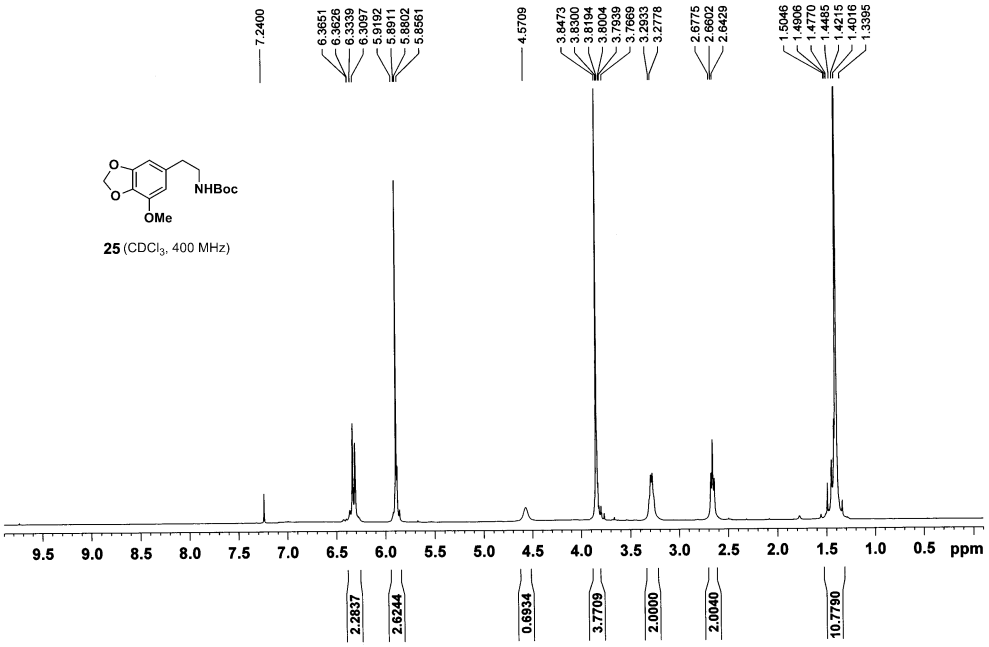


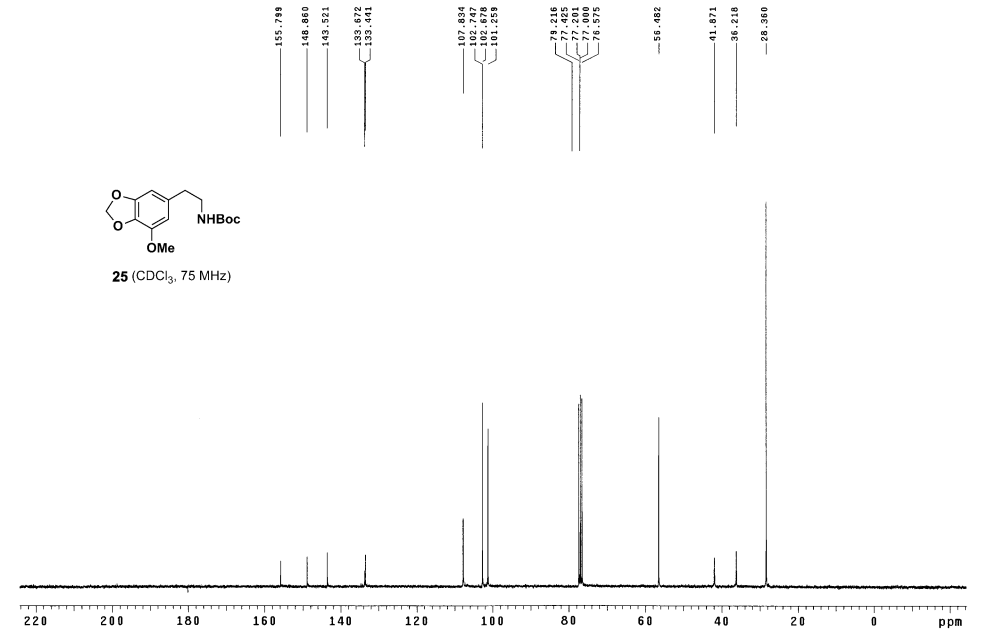


- ^{1}H-^{1}H COSY NMR spectrum of compound **37**

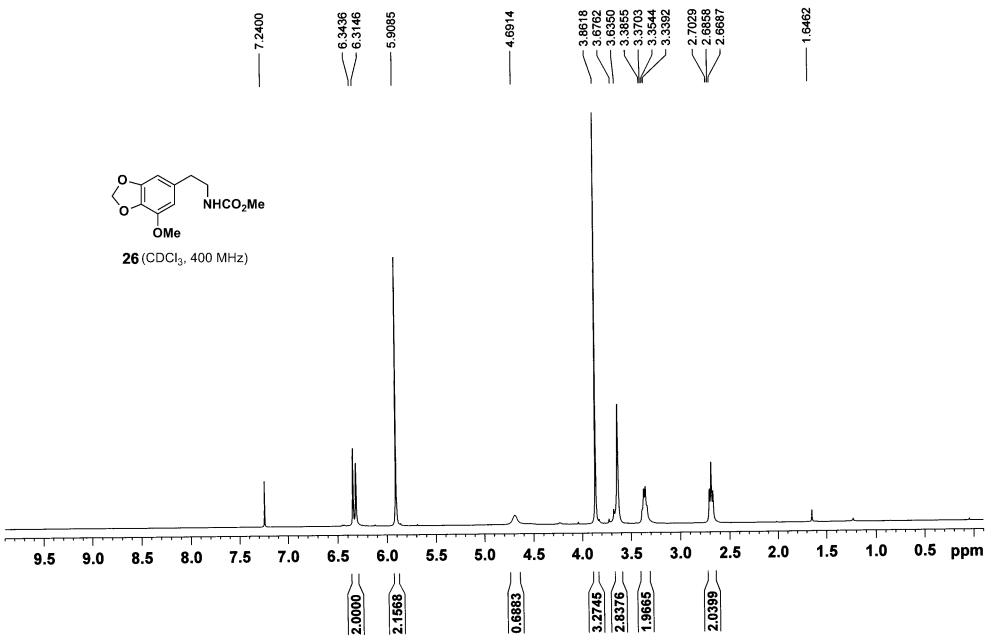


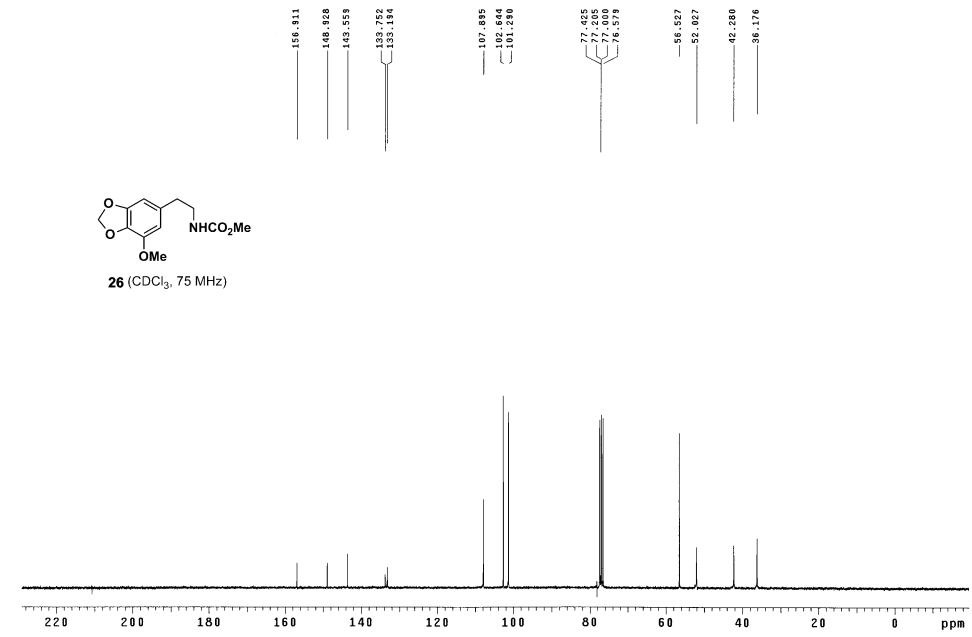
- ^{1}H & ^{13}C NMR spectrum of compound **25**



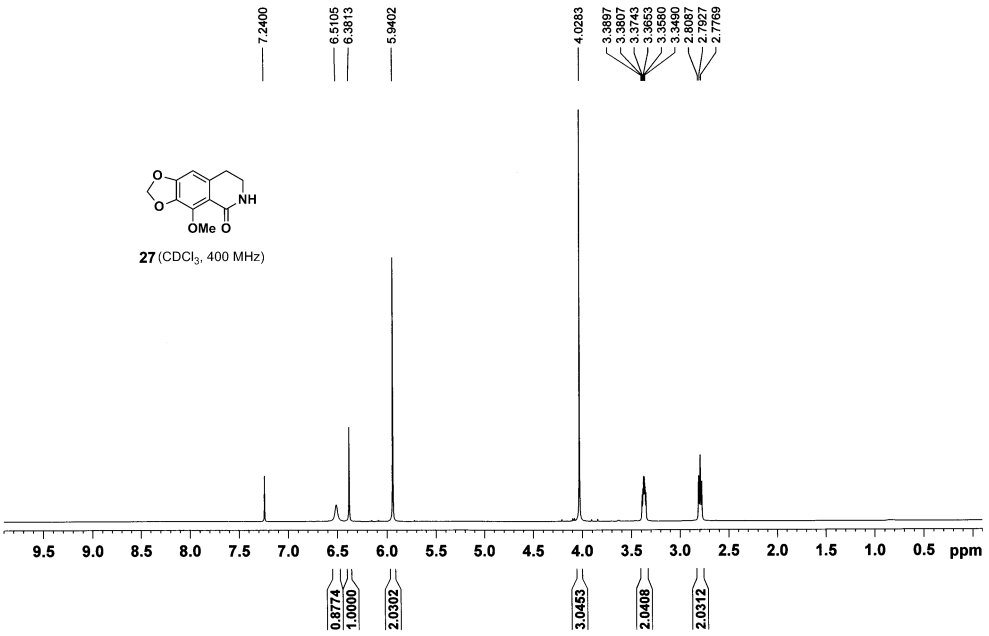


- ^{1}H & ^{13}C NMR spectrum of compound **26**

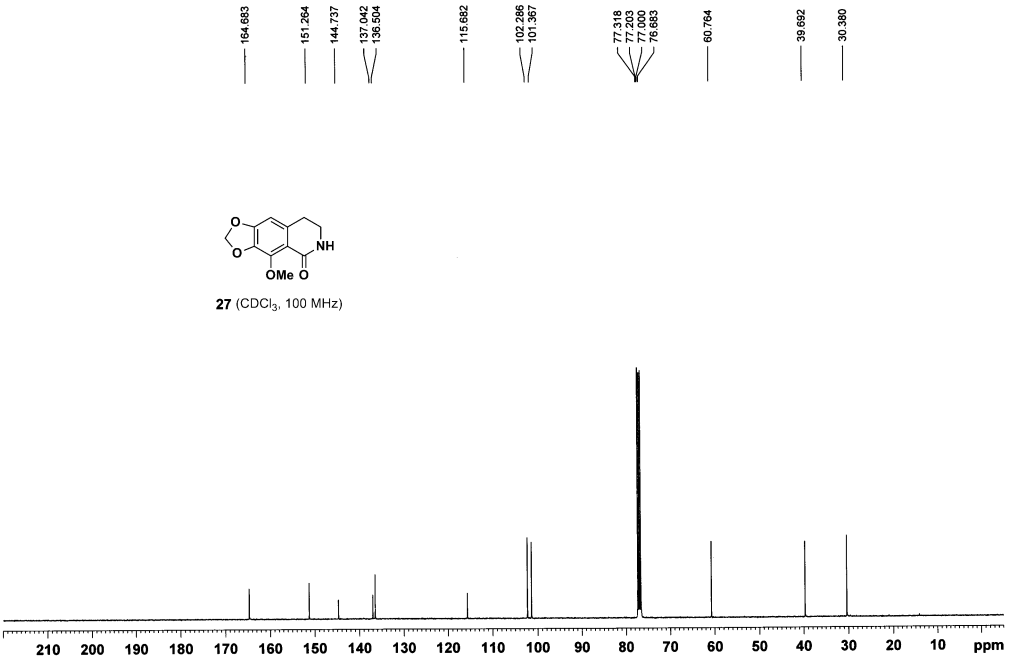




- ^{1}H & ^{13}C NMR spectrum of compound **27**

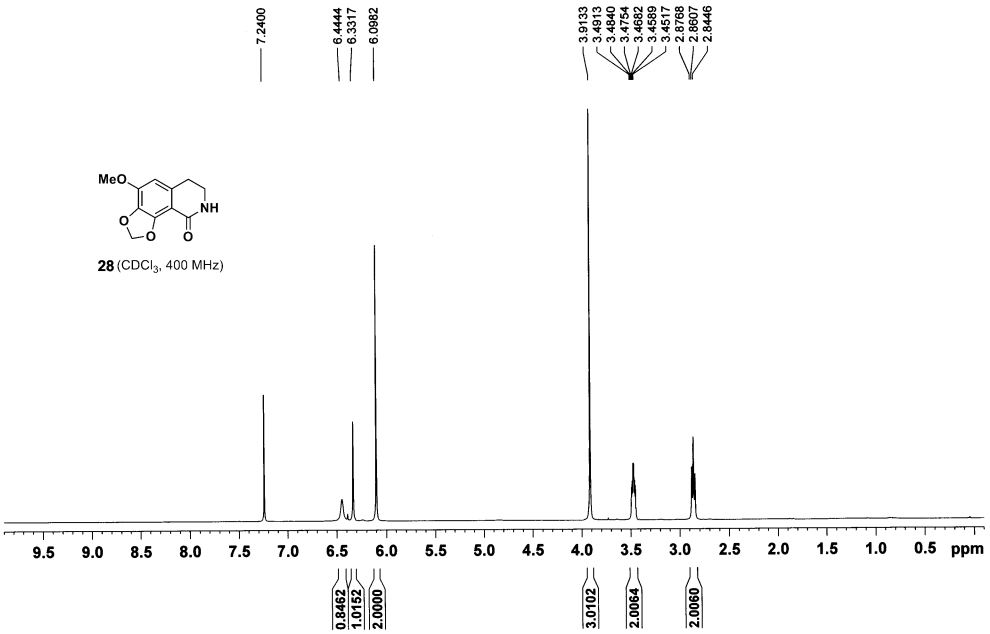


27 ($CDCl_3$, 400 MHz)

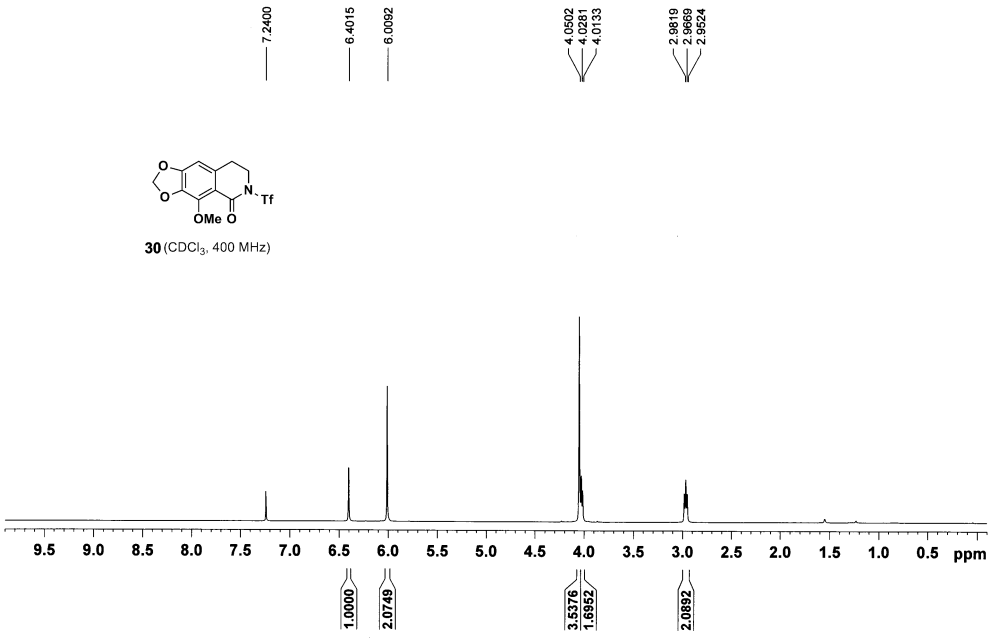


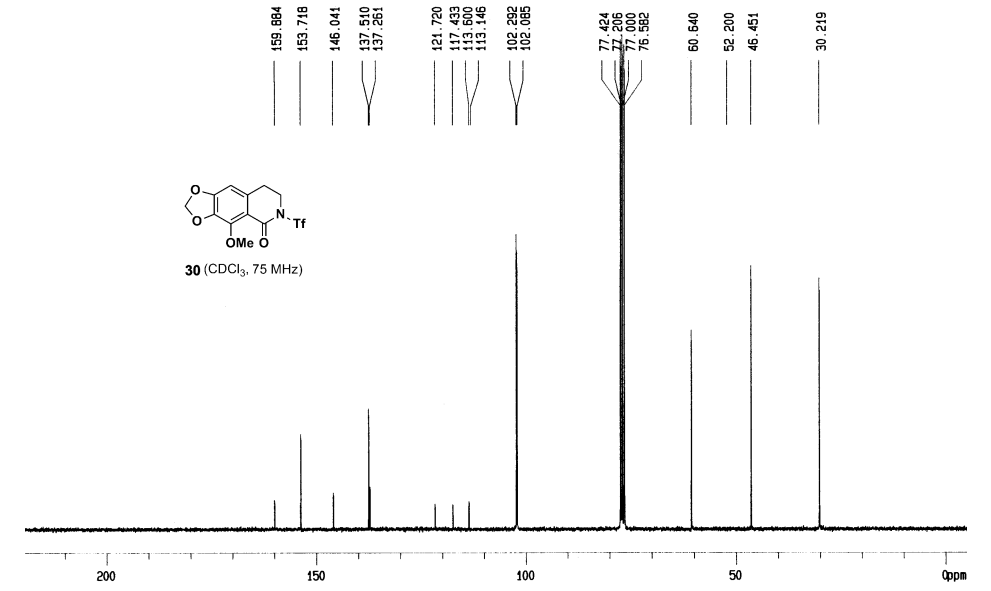
27 ($CDCl_3$, 100 MHz)

- ^{1}H NMR spectrum of compound **28**

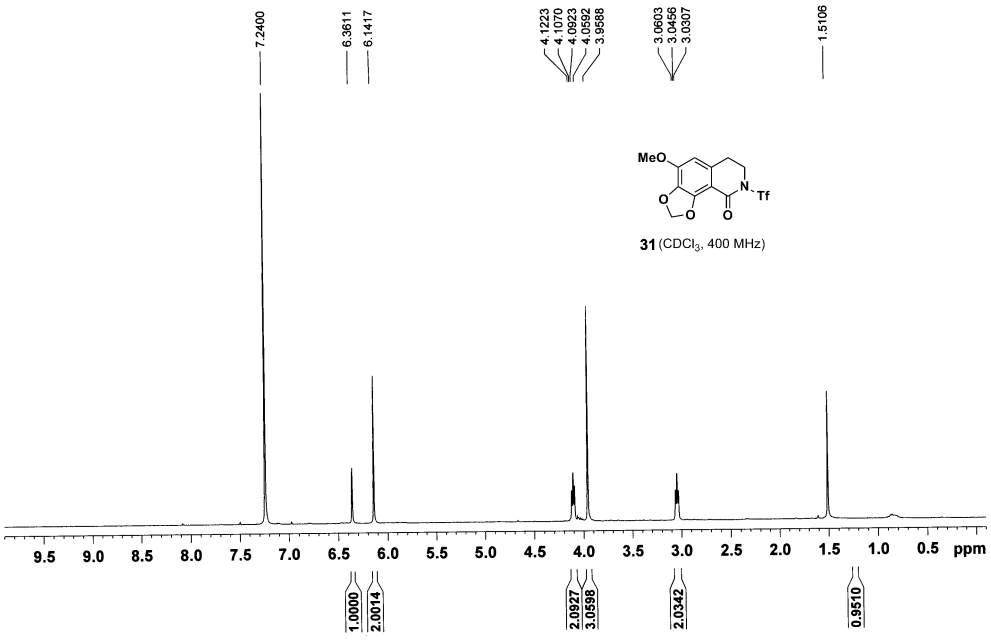


- ^{1}H & ^{13}C NMR spectrum of compound **30**

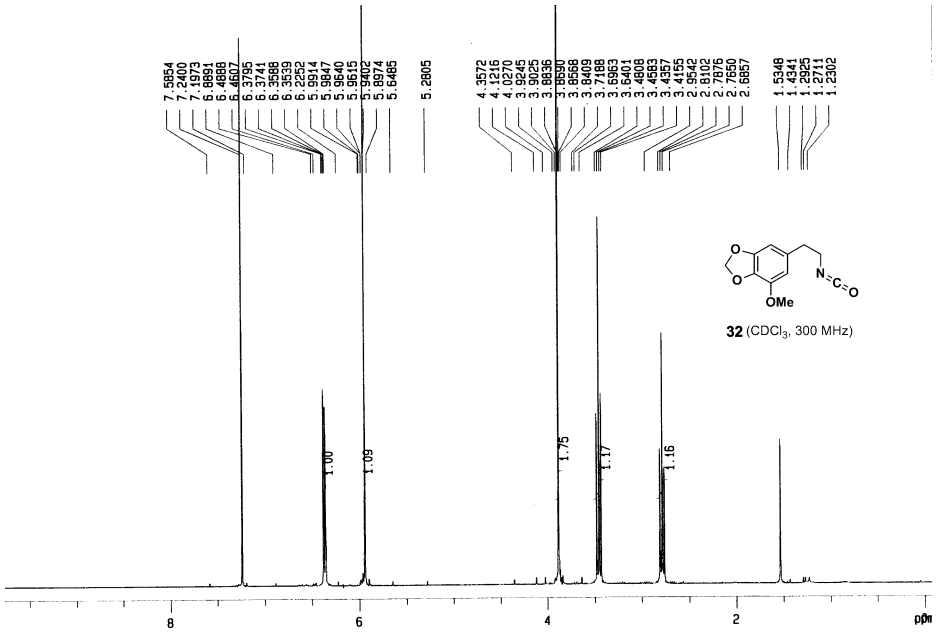


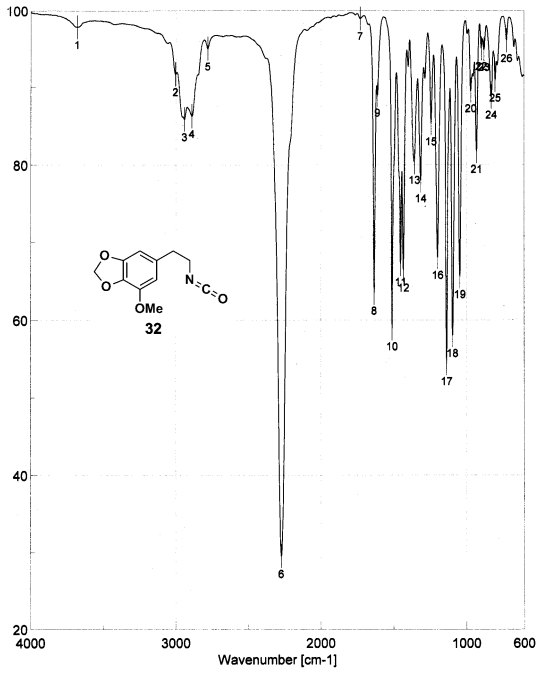


- ^{1}H NMR spectrum of compound **31**



- ^{1}H NMR & IR spectrum of compound **32**





[Comment]
Sample Name CH-IV-39 (isocyanate)
Comment
User
Division
Company SNU

[Data Information]
Creation Date 2012-02-07 오 5:27

Data array type Linear data array
Horizontal Wavenumber [cm-1]
Vertical %T
Start 599.753 cm-1
End 4000.6 cm-1
Data pitch 0.964233 cm-1
Data points 3528

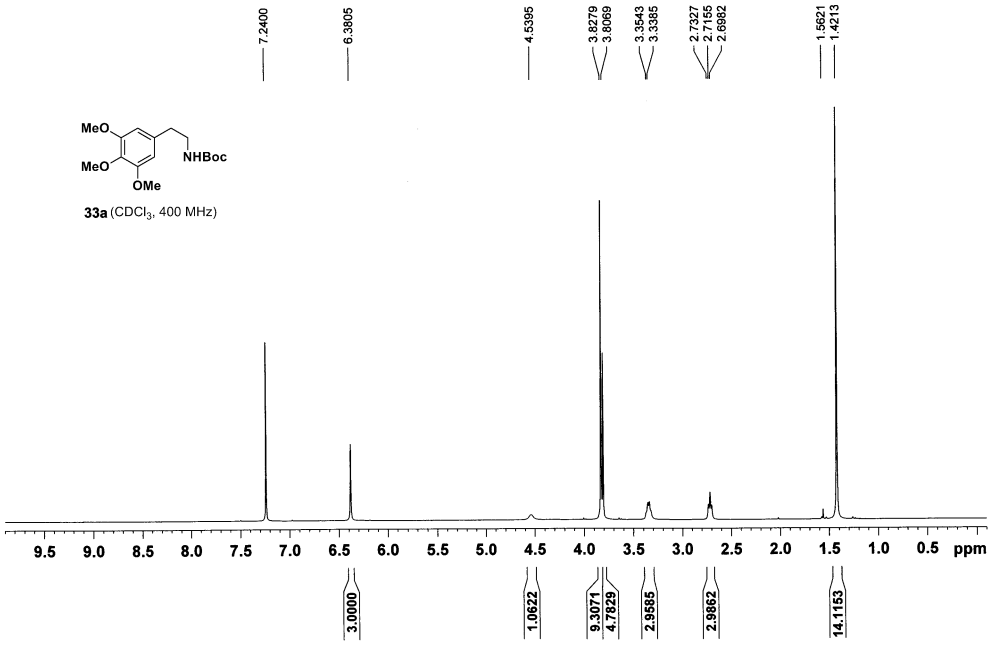
[Measurement Information]
Model Name FT/IR-4200typeA
Serial Number B038361018

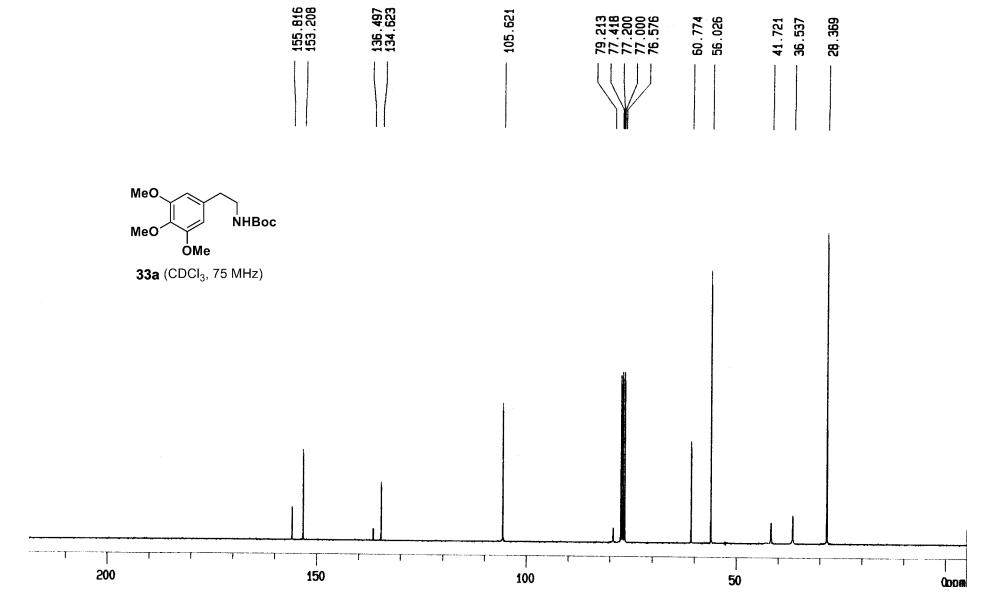
Light Source Standard
Detector TGS
Accumulation Auto (18)
Resolution 4 cm-1
Zero Filling On
Apodization Cosine
Gain Auto (2)
Aperture Auto (7.1 mm)
Scanning Speed Auto (2 mm/sec)
Filter Auto (30000 Hz)

Result of Peak Picking

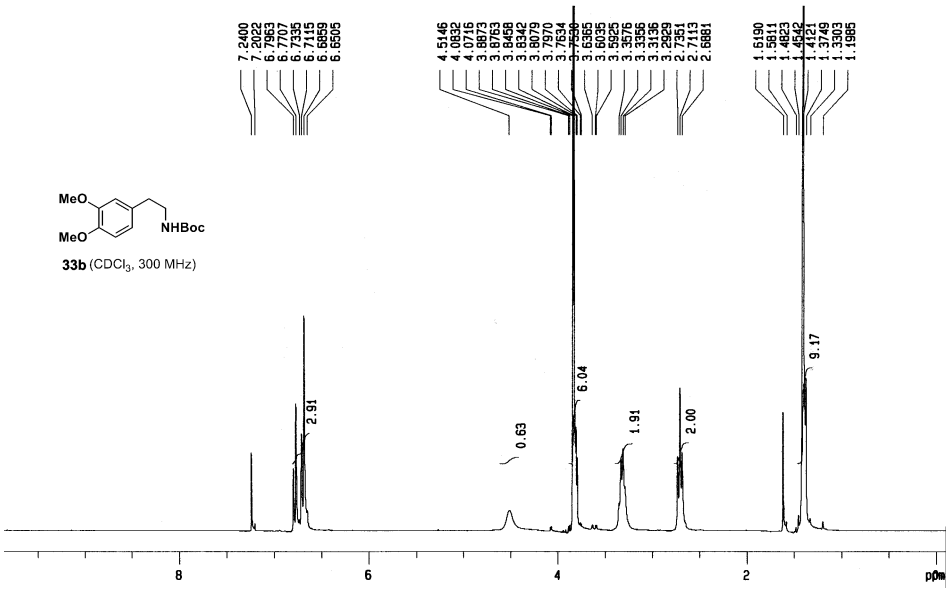
No.	Position	Intensity	No.	Position	Intensity
1	3682.41	97.8366	2	3004.55	91.6776
3	2942.84	85.8517	4	2891.74	86.2829
5	2781.81	95.0251	6	2273.66	29.5089
7	1731.76	98.9819	8	1634.38	63.5163
9	1612.2	89.0503	10	1511.92	58.9036
11	1452.14	67.2503	12	1432.85	66.4867
13	1357.64	80.3441	14	1313.29	77.9904
15	1241.93	85.3262	16	1196.61	68.1357
17	1133.94	54.3929	18	1093.44	58.0385
19	1044.26	65.6256	20	969.055	89.5679
21	929.521	81.7457	22	896.737	95.074
23	878.417	94.9228	24	827.312	88.7428
25	800.314	90.9463	26	722.211	96.0627

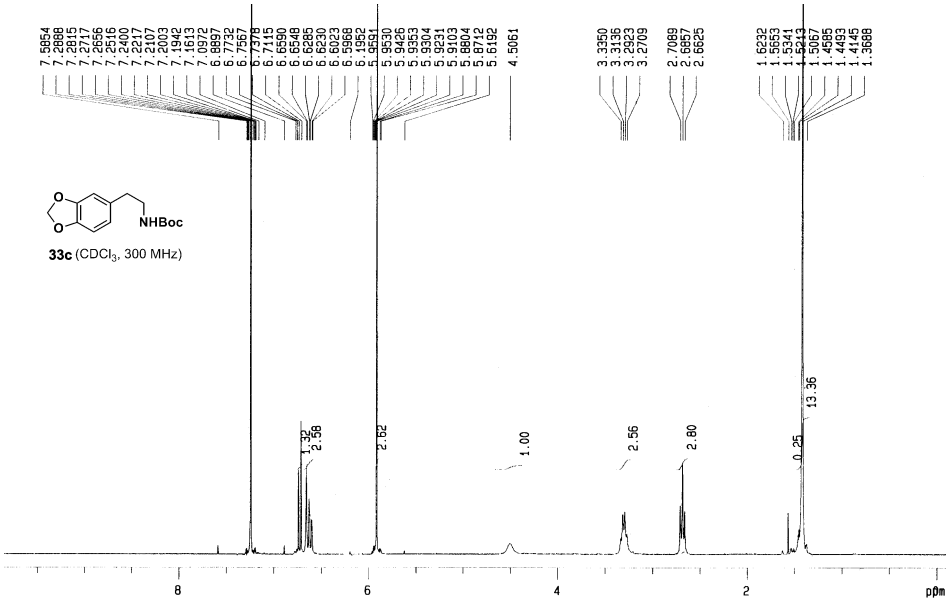
- ^{1}H & ^{13}C NMR spectrum of compound **33a**



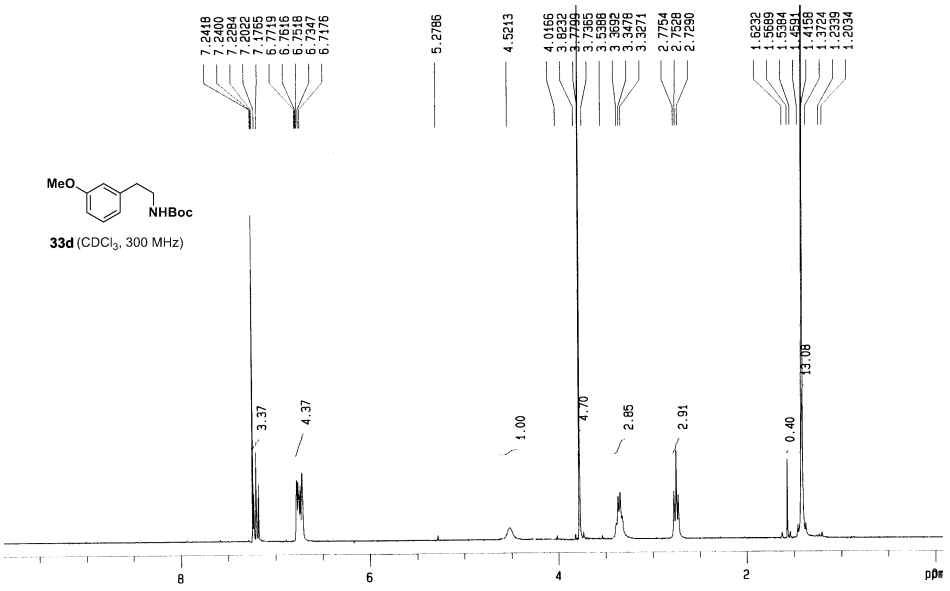


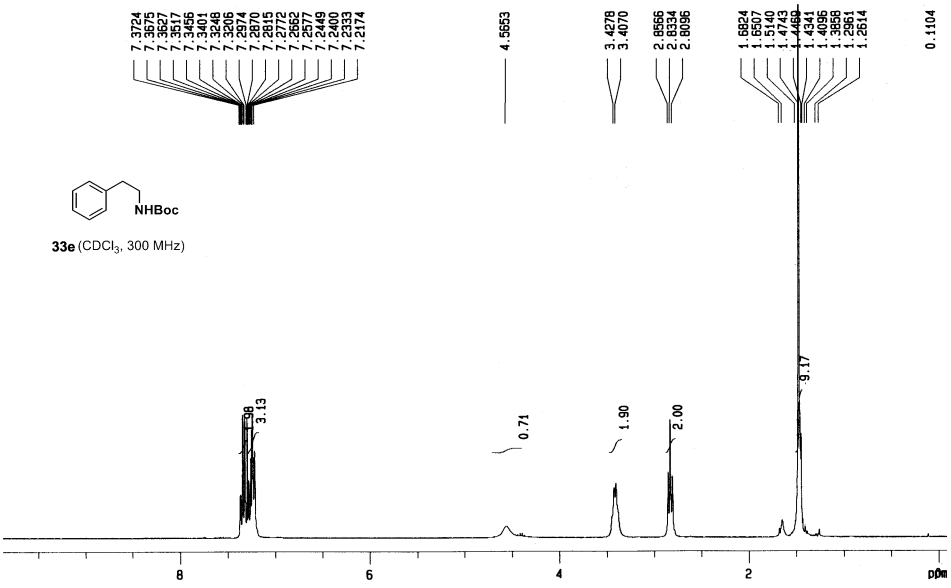
- ^{1}H NMR spectrum of compound **33b** and **33c**



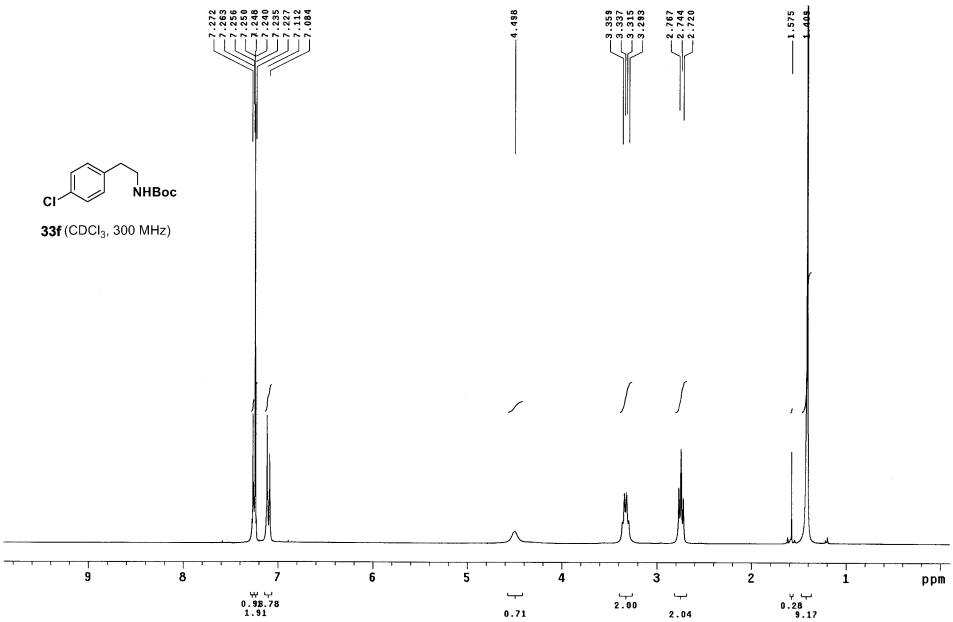


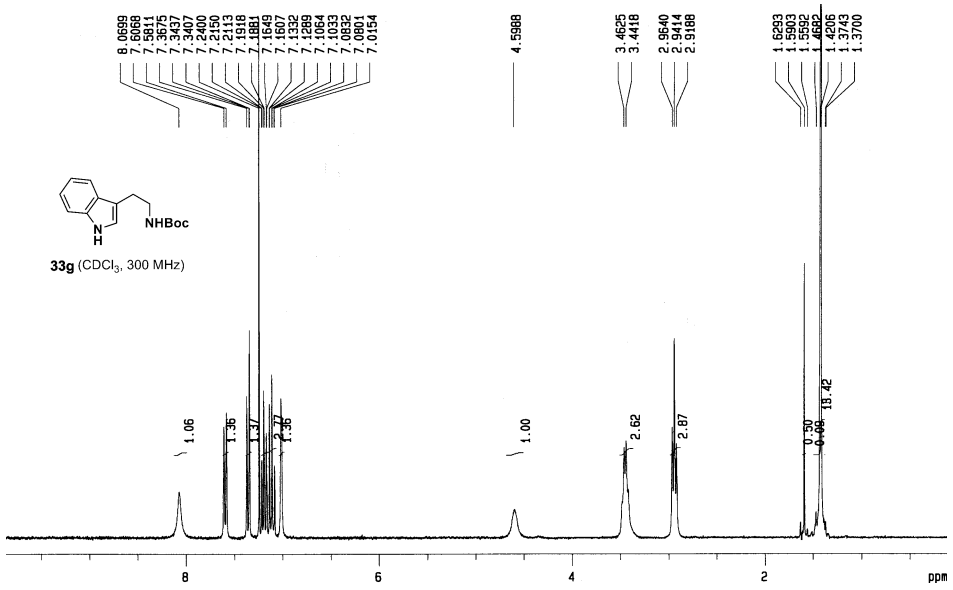
- ^{1}H NMR spectrum of compound **33d** and **33e**



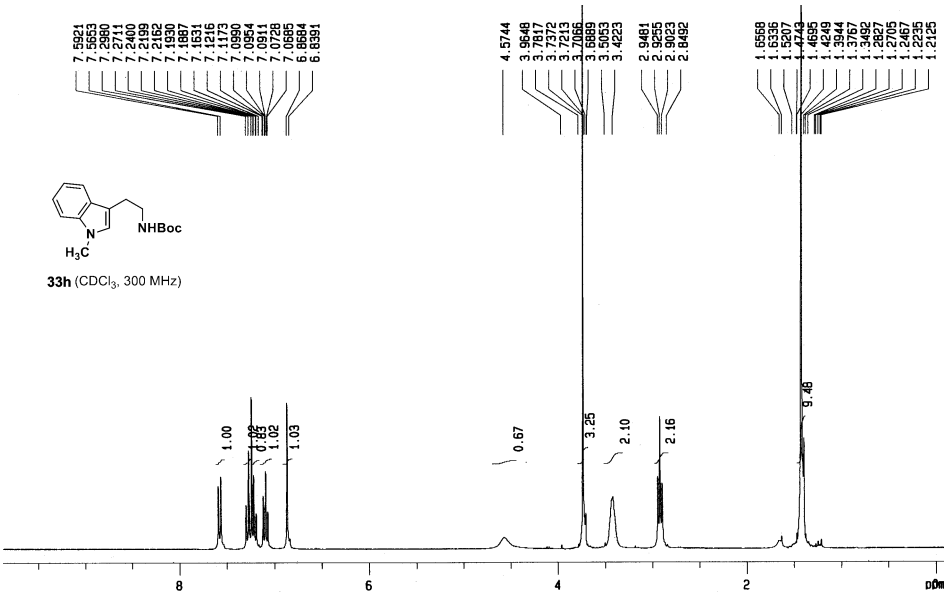


- ^{1}H NMR spectrum of compound **33f** and **33g**

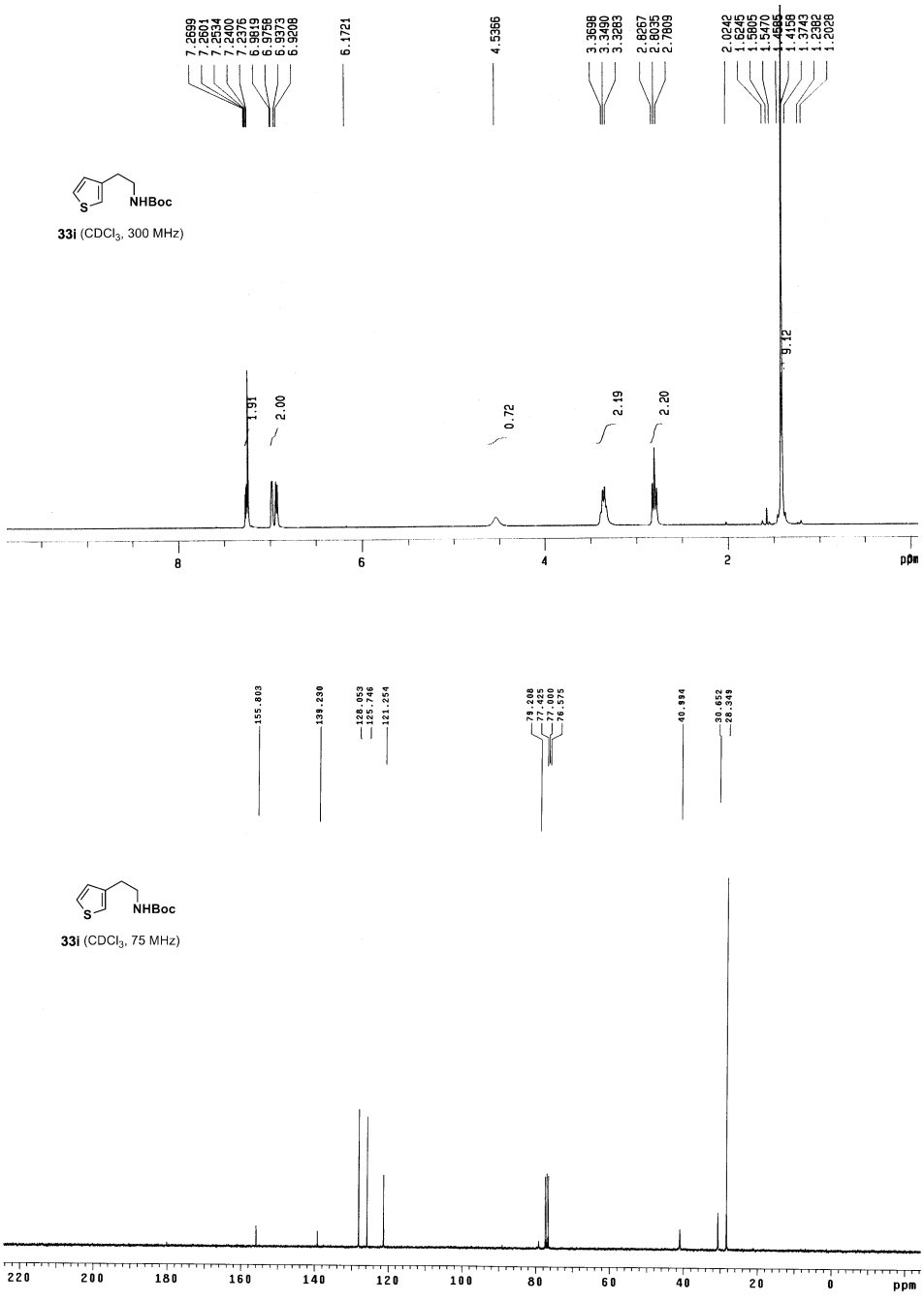




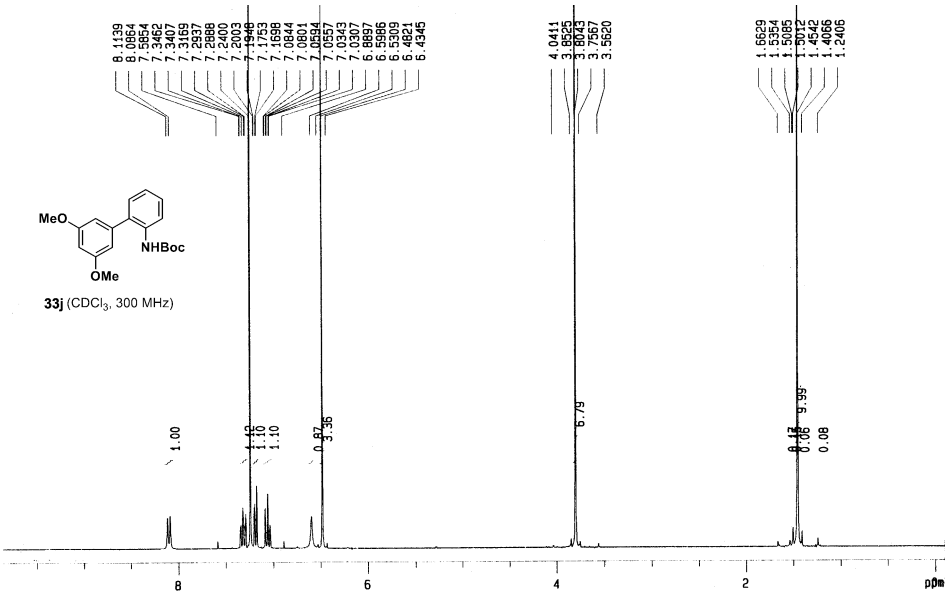
- ^{1}H NMR spectrum of compound **33h**



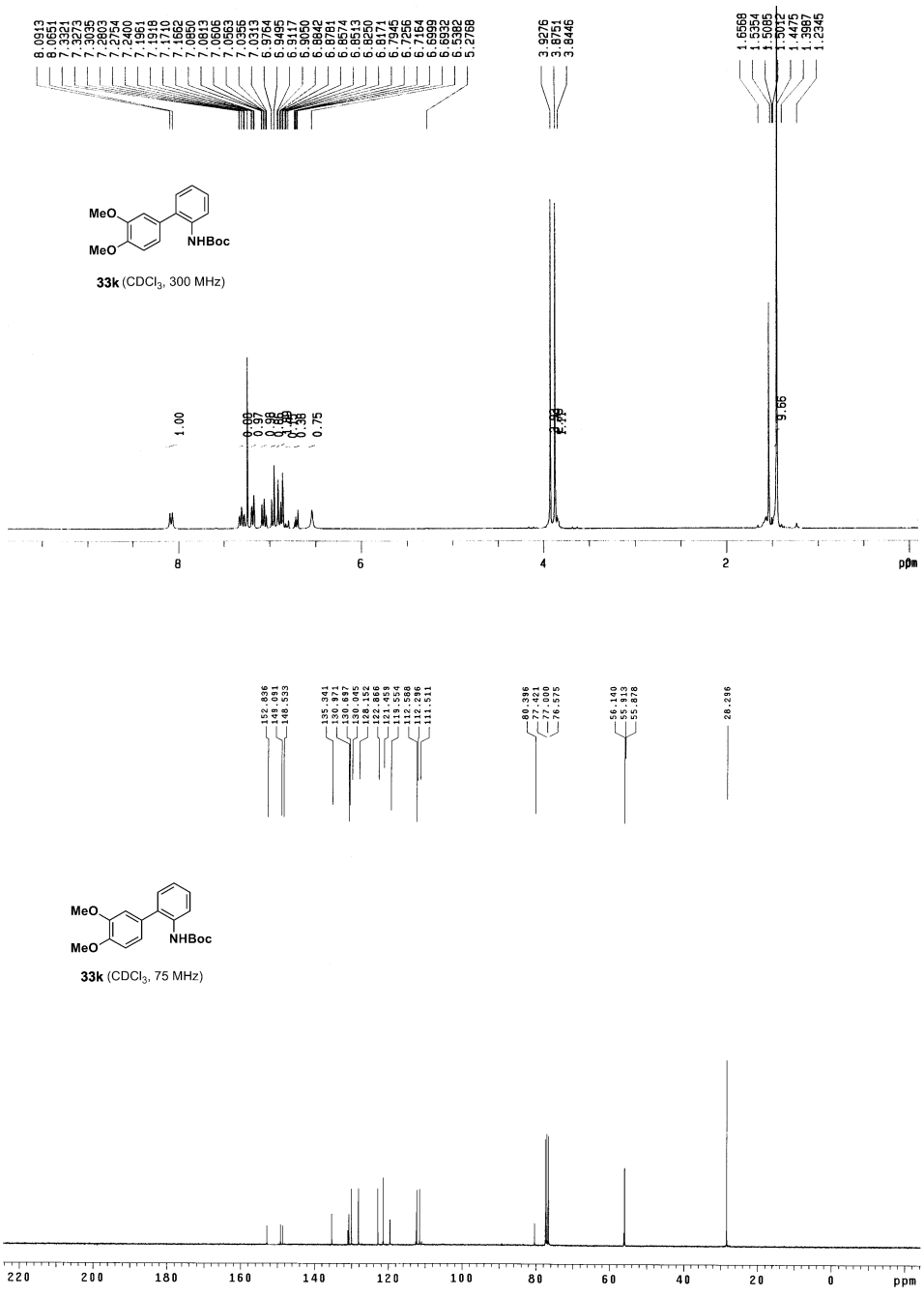
- ^{1}H & ^{13}C NMR spectrum of compound **33i**



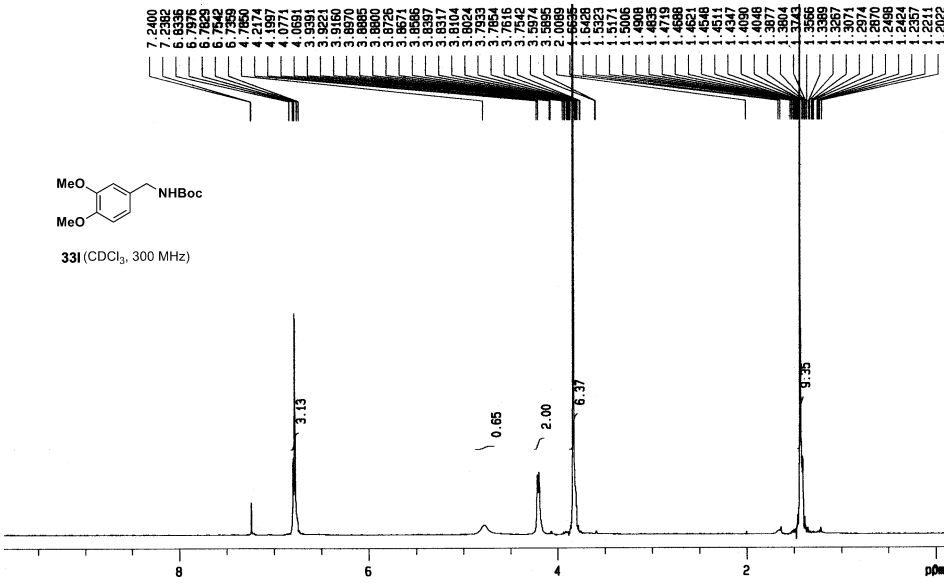
- ^{1}H NMR spectrum of compound **33j**



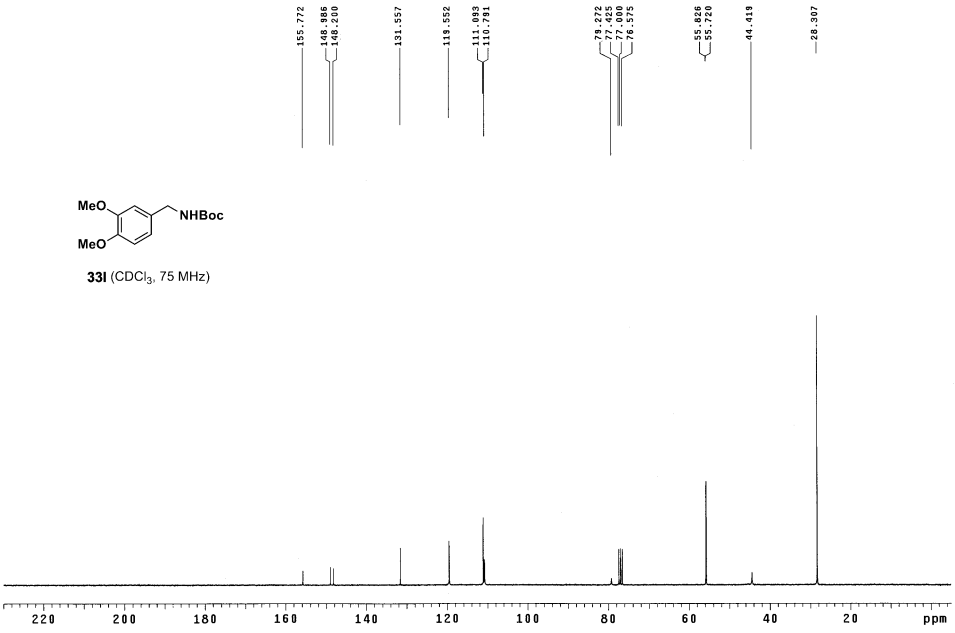
- ^{1}H & ^{13}C NMR spectrum of compound **33k**



- ^{1}H & ^{13}C NMR spectrum of compound **33l**

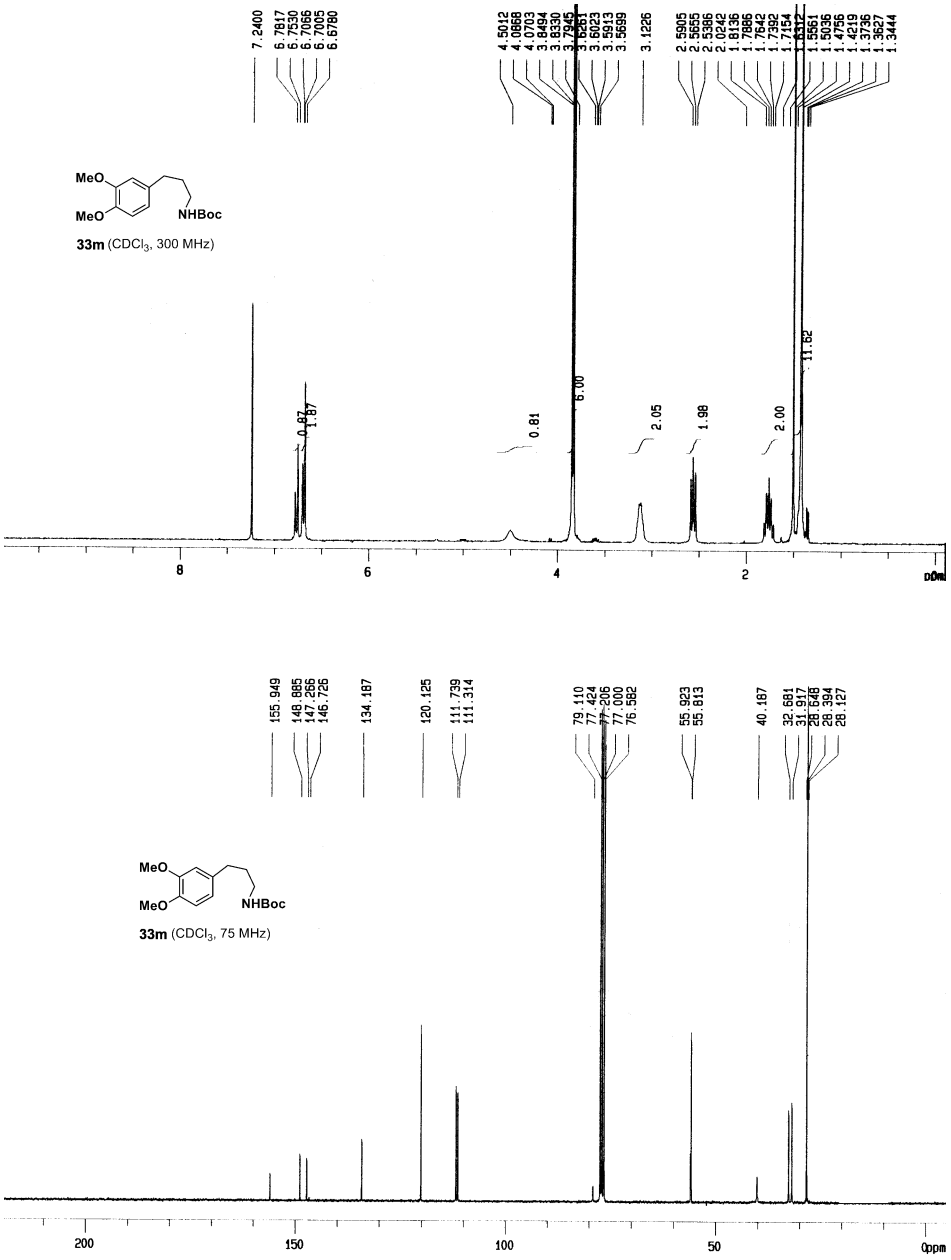


33l ($CDCl_3$, 300 MHz)

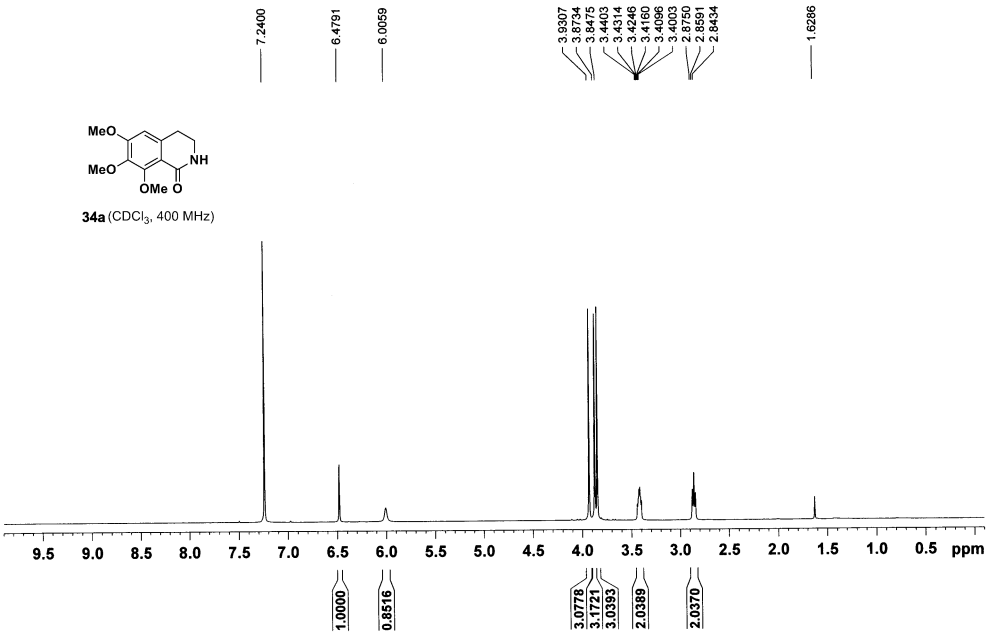


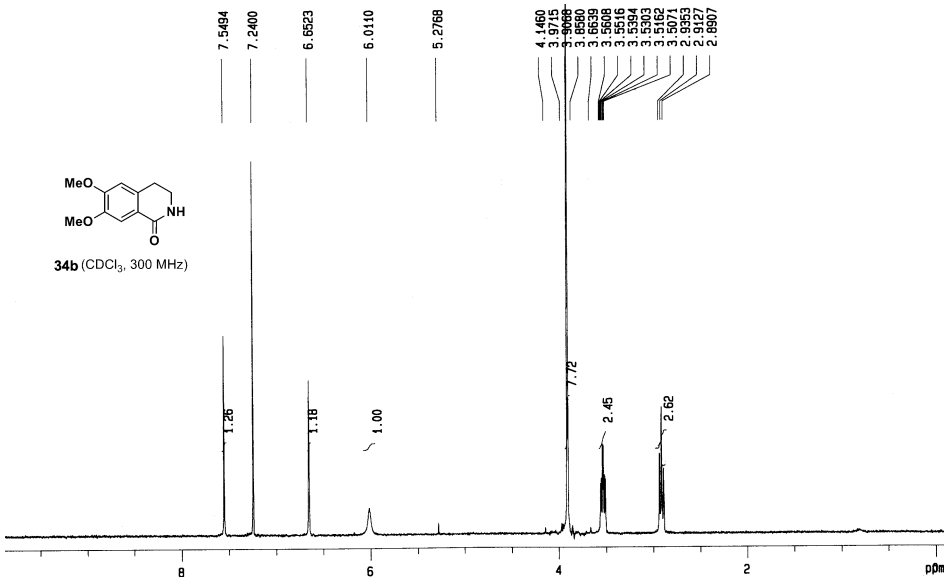
33l ($CDCl_3$, 75 MHz)

- ^{1}H & ^{13}C NMR spectrum of compound **33m**

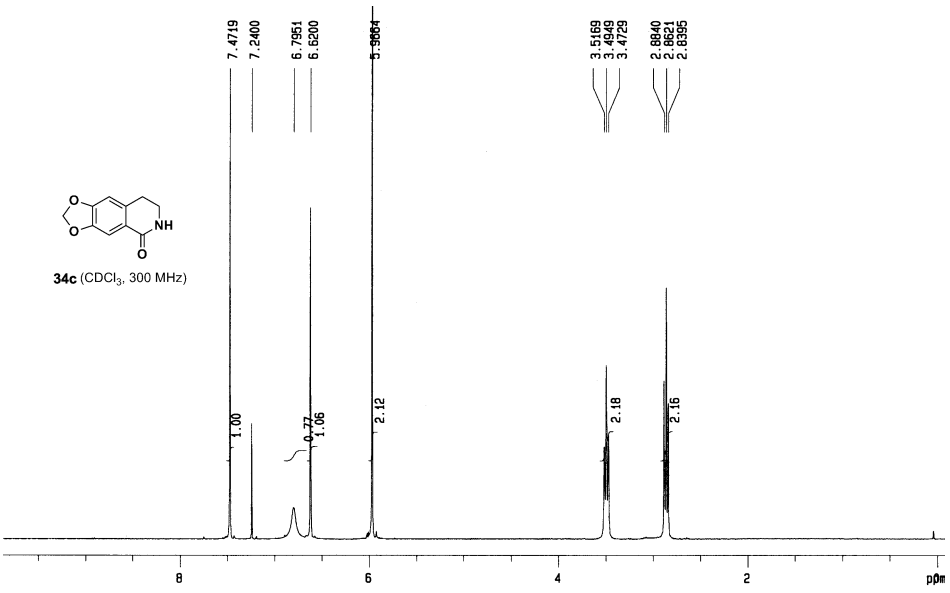


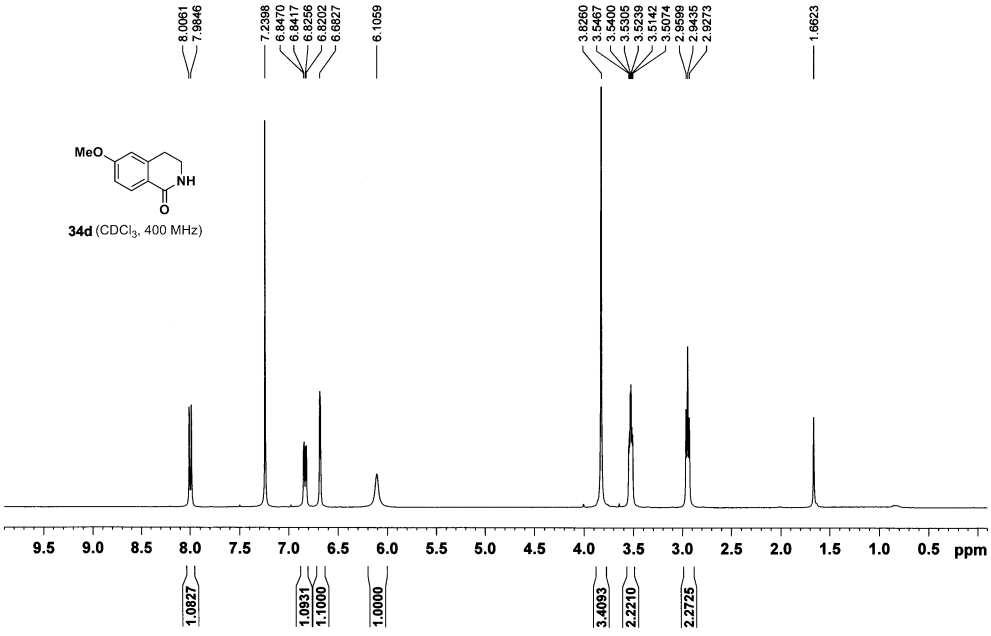
- ^{1}H NMR spectrum of compound **34a** and **34b**



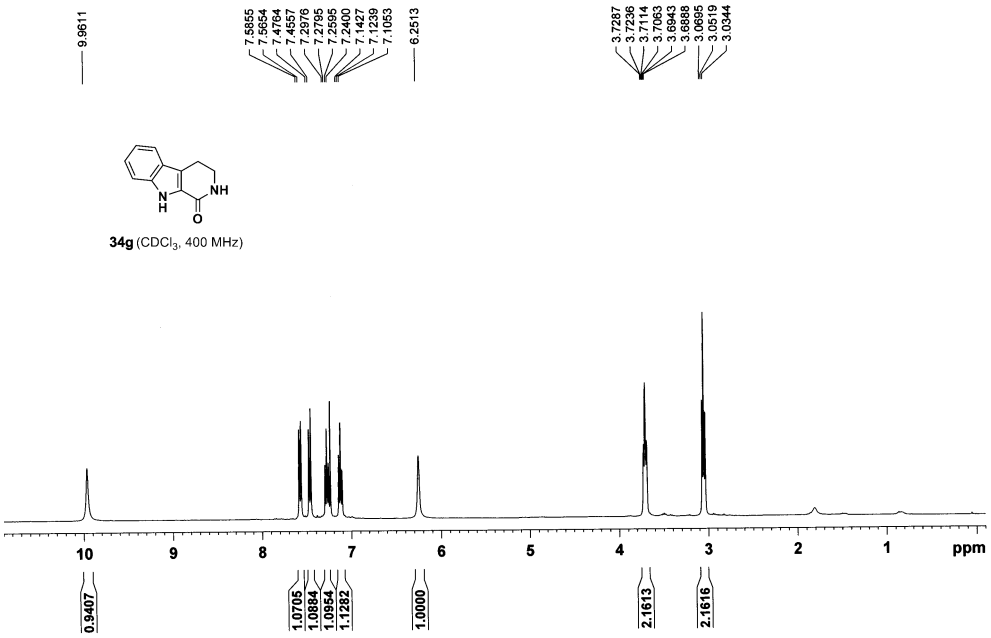


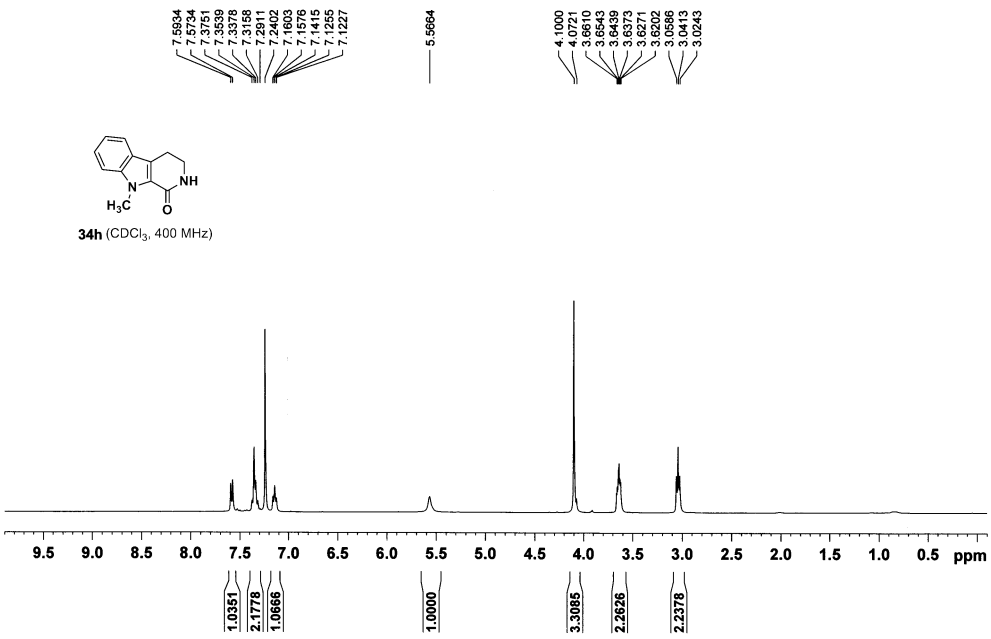
- ^{1}H NMR spectrum of compound **34c** and **34d**



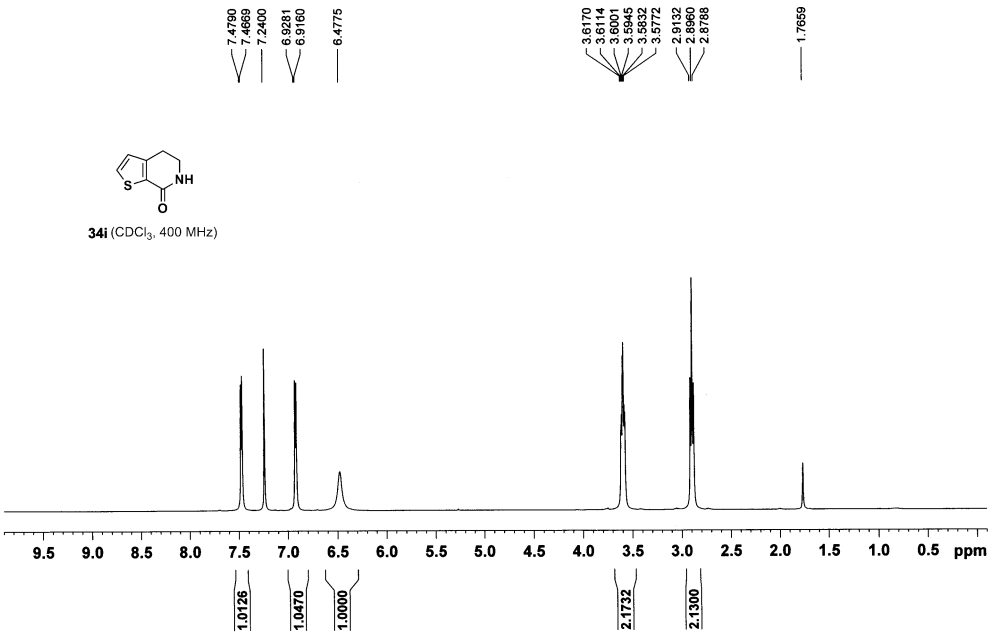


- ^{1}H NMR spectrum of compound **34g** and **34h**

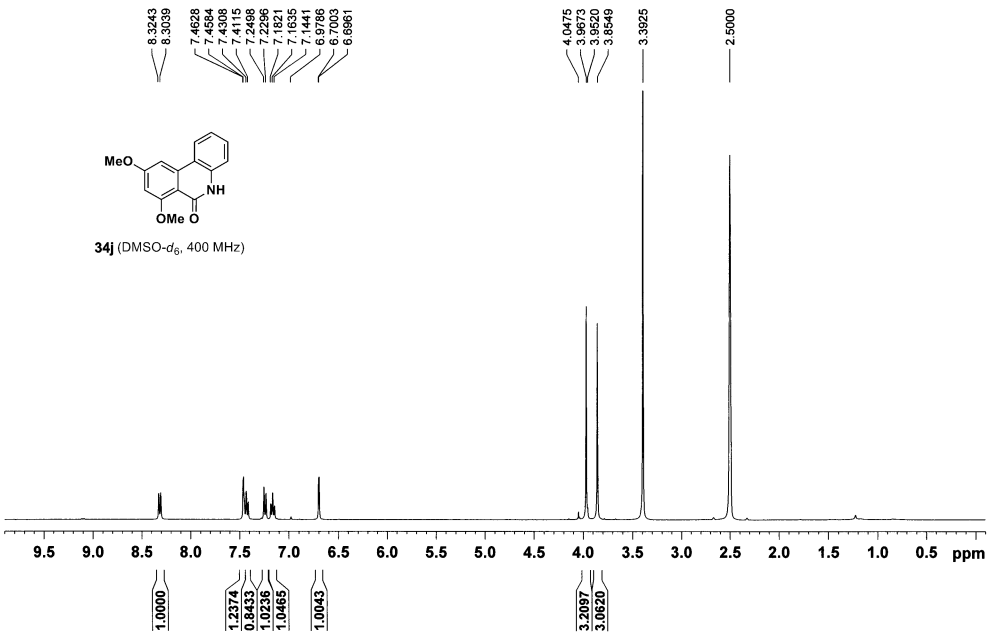




- ^{1}H NMR spectrum of compound **34i** and **34j**

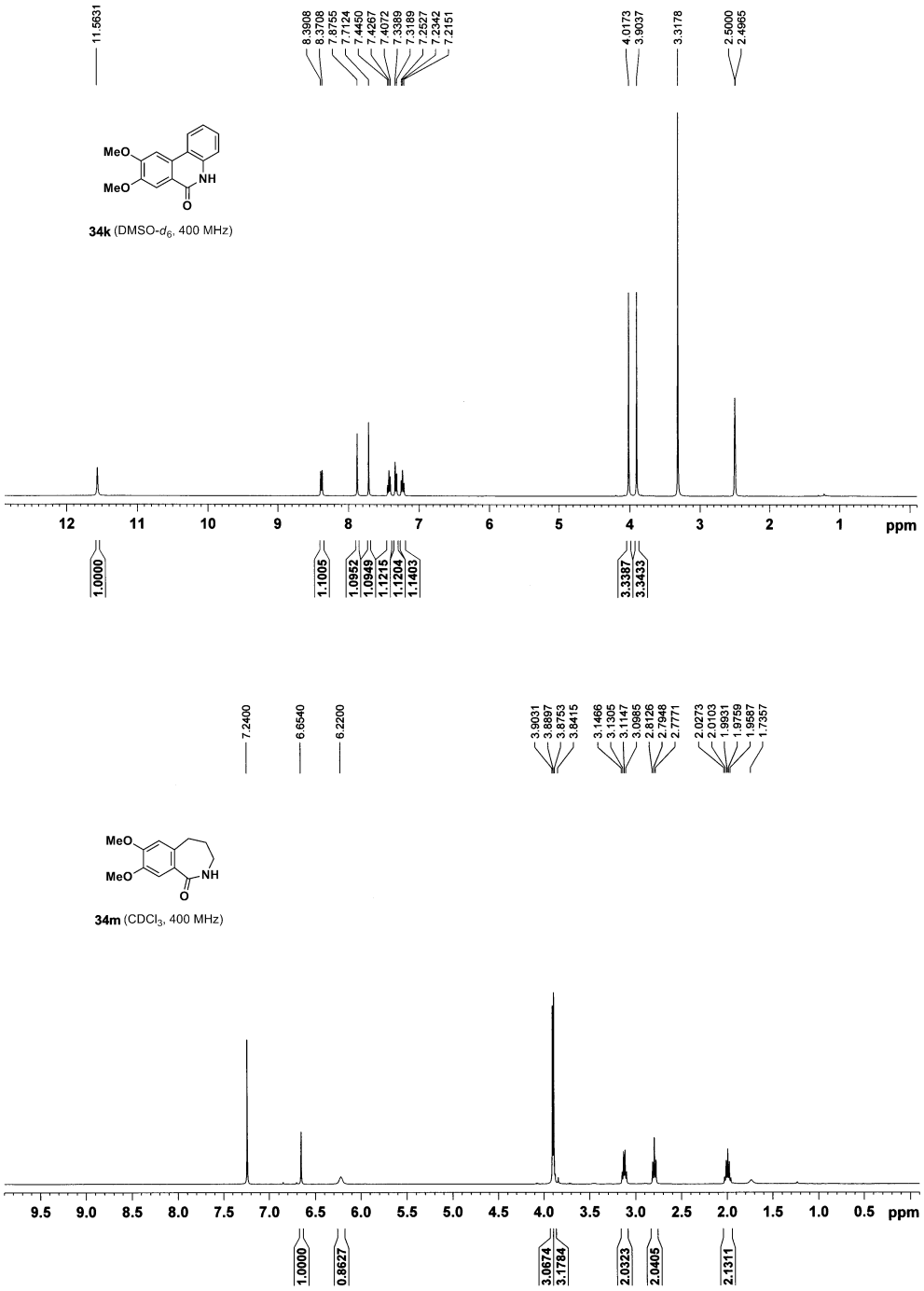


34i ($CDCl_3$, 400 MHz)



34j (DMSO-d_6, 400 MHz)

- ^{1}H NMR spectrum of compound **34k** and **34m**



Appendix II.

Publication List

(1) Cho, Jihee; Lee, Seokwoo; Hwang, Soonho; Kim, Sang Hoon; Kim, Jong Seung; Kim, Sanghee. "Calix[2]triazole[2]arenes; A Class of Hybrid Heterocalixarenes" *Eur. J. Org. Chem.* **2013**, 4614.

(2) In, Jinkyung[‡]; Hwang, Soonho[‡]; Kim, Changhun; Seo, Jae Hong; Kim, Sanghee. "Synthesis of 3,4-Dihydroisoquinolin-1-ones from *N*-Boc-(β-Arylethyl)-carbamates via Isocyanate Intermediates" *Eur. J. Org. Chem.* **2013**, 965. ([‡] These two authors contributed equally to this work.)

(3) Hwang, Soonho; Bae, Hoon; Kim, Sumin; Kim, Sanghee. "An efficient and high-yielding one-pot synthesis of 4-acyl-1,2,3-triazoles via triisopropylsilyl-protected ynones" *Tetrahedron* **2012**, *68*, 1460.

(4) Hwang, Soonho; Kim, Deukjoon; Kim, Sanghee. "Stereocontrolled Total Synthesis of (+)-*trans*-Dihydronarciclasine" *Chem. Eur. J.* **2012**, *18*, 9977.

(5) Lee, Eun-Jung; Lee, Yun Sang; Hwang, Soonho; Kim, Sanghee; Hwang, Jae Sung; Kim, Tae-Yoon. "*N*-(3,5-Dimethylphenyl)-3-Methoxybenzamide (A_3B_5) Targets TRP-2 and Inhibits Melanogenesis and Melanoma Growth" *J. Invest. Dermatol.* **2011**, *131*, 1701.

(6) Hwang, Soonho; Kim, Jae Hyun; Kim, Hak Sung; Kim, Sanghee. "Total Synthesis of the Proposed Structure of Trocheliophorolide D" *Eur. J. Org. Chem.* **2011**, 7414.

(7) Lee, Hyun-Ji; Lim, Chaemin; Hwang, Soonho; Jeong, Byeong-Seon; Kim, Sanghee. "Silver-Mediated *exo*-Selective Tandem Desilylative Bromination/Oxycyclization of Silyl-Protected Alkynes: Synthesis of 2-Bromomethylene-Tetrahydrofuran" *Chem.*

Asian J. **2011**, *6*, 1943.

(8) Lee, Seokwoo; Hwang, Soonho; Yu, Shuai; Jang, Wonyoung; Lee, Yun Mi; Kim, Sanghee. "Synthesis and Evaluation of C-ring Aromatized Analogues of Phenanthridone Alkaloids" *Arch. Pharm. Res.* **2011**, *34*, 1065.

(9) Hwang, Soonho; Choi, Sang Yoon; Lee, Jin Hee; Kim, Shinae; In, Jinkyung; Ha, Sang Keun; Lee, Eunjung; Kim, Tae-Yoon; Kim, Sun Yeou; Choi, Sun; Kim, Sanghee. "Identification of a potent and noncytotoxic inhibitor of melanin production" *Bioorg. Med. Chem.* **2010**, *18*, 5602.

(10) Hwang, Soonho; Kang, Hee Ryung; Kim, Sanghee. "Synthesis of polyynes by in situ desilylative bromination and palladium-catalyzed coupling: (7-benzyloxy)hepta-1,3,5-triynyl)triisopropylsilane" *Org. Synth.* **2009**, *86*, 225.

(11) Song, Yanling; Hwnag, Soonho; Gong, Ping; Kim, Deukjoon, Kim, Sanghee. "Stereoselective Total Synthesis of (-)-Perrottetinene and Assignment of Its Absolute Configuration" *Org. Lett.* **2008**, *10*, 269.

국 문 초 록

(+)-*trans*-Dihydronarciclasine은 Amaryllidaceae isocarbostyril 알칼로이드 계열에 속하는 대표적인 화합물로서 다양한 암세포주에 대해 강력하고 선택적인 항암활성을 보인다고 알려져 있다.

본 논문은 쉽게 이용 가능한 시작물질로부터 매우 입체선택적이며 효과적인 합성법으로 (+)-*trans*-dihydronarciclasine의 비대칭 전합성을 수행하는 과정에 대해 제시하는 논문이다.

광학적으로 순수한 시작물질인 allylic alcohol은 cross-coupling 반응과 효소에 의한 광학분할 방법을 이용해 얻을 수 있었으며, 본 합성의 핵심 중간체인 vinylogous ester는 allylic ester로부터 amino acid ester-enolate Claisen rearrangement와 위치선택적인 Wacker oxidation, Dieckmann 축합반응을 통해 합성할 수 있었다. 이로부터 입체선택적인 산화-환원 반응을 거쳐 원하는 입체화학을 갖는 C-ring을 합성할 수 있었다.

특히 B-ring의 합성은 *N*-Boc carbamate로부터 합성된 isocyanate 중간체를 통한 Friedel-Crafts-type 고리화 반응을 통해, 기존에 본 계열 천연물의 합성에 많이 이용되는 Bischler-Napieralski 반응을 통한 고리화 반응의 낮은 선택성 문제를 해결하면서 효과적으로 수행할 수 있었다. 이 과정에서 얻어진 반응 조건은 다양한 3,4-dihydroisoquinolinone 및 관련된 heterocycle의 화합물 합성에도 응용 가능함을 확인하였다.

주요어: Acid-mediated cyclization, Antitumor agents, Ireland-Claisen rearrangement, Natural products, Total synthesis

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